

인사말

안녕하십니까? 반갑습니다.

따스한 가을 햇살 아래에 추수의 기쁨을 가지는 11월 의약품 업계 관계자분들에게 인사를 드리게 되어 기쁘게 생각합니다.

식품의약품안전청은 국민에게 보다 안전하고 우수한 품질의 의약품 생산 공급 기반을 마련하기 위한 GMP 규제 합리화로 제약산업의 국제 경쟁력 강화를 지원하고 있으며, 우수 의약품 제조기반 확대, 국제조화 및 의약품 해외수출 활성화를 위한 적극적인 GMP 정책지원, GMP 평가 업무의 효율성 제고 및 전문성 강화를 모색하고 있습니다.

이를 위하여 식품의약품안전평가원에서는 국내외 GMP 규정, 지침서 및 연구 동향을 조사·분석하여 국제적인 의약품 GMP 규정과 조화되는 품질관리 시스템 구축을 위한 과학적인 지원을 하고 있습니다. 또한 의약품 GMP 조사관 및 직원들의 업무 역량 향상을 위하여 의약품 GMP 온라인 교육 시스템 체계를 구축하고 있습니다.

최근 미국 FDA, EU, EMA, WHO 등에서는 의약품 GMP 가이드라인을 지속적으로 개정 및 발간하는 등 우수품질 의약품 확보를 위한 노력을 기울이고 있으며, 이에 식품의약품안전평가원에서는 GMP 규정의 국제조화 기반마련 및 해외수출 업체에게 정보제공을 위하여 “국외 의약품 GMP 가이드라인 동향 모음집”을 발간하게 되었습니다.

본 “국외 의약품 GMP 가이드라인 동향 모음집”이 국내 GMP 관련 업무 종사자들에게 유용한 자료로 활용되기를 바라며, 나아가 국민들에게 우수한 품질의 의약품이 제공되고 제약산업 경쟁력 강화에 도움이 될 수 있기를 기대합니다. 식품의약품안전평가원은 앞으로도 국내 의약품 제조품질관리기준의 국제조화 및 의약품 품질 향상을 위한 지속적인 노력을 하겠습니다.

감사합니다.

2011년 11월

식품의약품안전평가원장 **김 승 희**

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서론

의약품 제조품질관리기준(GMP)은 우수한 품질이 보장된 의약품을 제조·공급하기 위해 제조소의 구조·설비를 비롯하여, 의약품의 원료·자재 등의 구입부터 제조·포장 등 모든 공정관리와 출하에 이르는 제조 및 품질관리 전반에 걸쳐 지켜야 할 사항을 규정한 기준이다. 또한 의약품이 약사법에 따른 안전성과 유효성을 확보할 수 있도록 우수한 품질로 일관성 있게 제조됨을 보증하기 위하여 관련시설, 방법 및 관리의 운영 및 시행에 대하여 정한 최소한의 기준이다.

의약품 GMP는 안전성·유효성 및 안정성이 확보되어야 하는 의약품의 특수한 요구 조건을 만족시키기 위한 종합적 품질관리 체계가 요구되어지며 의약품 제조시 발생 할 수 있는 과오 및 품질저하를 예방하기 위해 공정의 첫 단계부터 각종 점검, 검사 및 시험절차 설계와 제조공정 변경시 품질 유지를 위한 시험 및 점검 체계가 필요하다.

2011년 11월 현재 EU GMP는 3개 파트(의약품, 원료의약품, 기타)와 1개의 Annex(19개 문서)로 구성되어 있으며 EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines에 가이드라인들이 정리되어 있다. WHO GMP는 4개 파트 : WHO good manufacturing practices(15개 문서), Risk analysis(1개 문서), Technology transfer(1개 문서), Training materials(2개 문서)로 구성되어 있다. EMA GMP는 10개의 파트(92개 문서)로 구성되어 가이드라인이 정리되어 있다. FDA GMP 관련 가이드는 39개가 있다.

본 “국외 의약품 GMP 가이드라인 동향 모음집”은 각국의 GMP 가이드라인의 구성 내용을 소개하고 '10년 7월부터 1년간의 미국 FDA, EU, EMA, WHO 등의 가이드라인 개정 및 발간사항을 분석하여 정리하였다.



의약품 GMP 가이드라인 비교

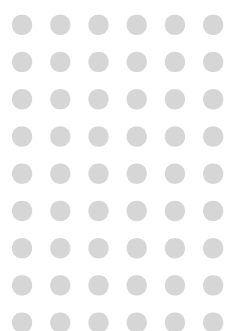
카테고리	세부 주제	FDA	EMA	PIC/S	WHO	ICH
1. GMP 일반	GMP 조직/시스템	Quality System Approach to Pharmaceutical Current Good Manufacturing Practice Regulations	GMP Guide Annex 16: Certification by a Qualified Person and Batch Release	PIC/S GMP Guides part1	Authorized Person – Role, Functions, and Training, Annex 4, TRS No. 885, 1999	Q10 Pharmaceutical Quality System
	품질 리스크 관리		GMP Guide Annex 20: Quality Risk Management		Application of HACCP Methodology to Pharmaceuticals, Annex 7, TRS No. 908, 2003	Q9 Quality Risk Management
	PAT	PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance				
	의약품 개발					Q8 Pharmaceutical Development Annex to Q8 Pharmaceutical Development
	임상 의약품	Guideline on the Preparation of Investigational New Drug Products (Human and Animal) INDs – Approaches to Complying with CGMP During Phase 1	GMP Guide Annex 13: Manufacture of Investigational Medicinal Products	GMP Guide Annex 13: Manufacture of Investigational Medicinal Products		
	무균 제제	Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice	GMP Guide Annex 1: Manufacture of Sterile Medicinal Products	GMP Guide Annex 1: Manufacture of Sterile Medicinal Products	GMP for Sterile Pharmaceutical Products, Annex 6, TRS No. 902, 2002	
	방사성 의약품		GMP Guide Annex 3: Manufacture of Radiopharmaceuticals	GMP Guide Annex 3: Manufacture of Radiopharmaceuticals	GMP for Radiopharmaceutical Products, Annex 3, TRS No. 908, 2003	
	액제, 크림제, 연고제		GMP Guide Annex 9: Manufacture of Liquids, Creams and Ointments	GMP Guide Annex 9: Manufacture of Liquids, Creams and Ointments		
	의료용 고압가스	Compressed medicinal gas guidance, 2005	Guideline on Medicinal gases, 2007	Manufacture of medicinal gases		
	에어로솔제		GMP Guide Annex 10: Manufacture of Pressurized Metered Dose Aerosol Preparations for Inhalation	GMP Guide Annex 10: Manufacture of Pressurized Metered Dose Aerosol Preparations for Inhalation		
2. GMP 시설설비	HVAC 시스템				Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms, Annex 2, TRS No. 937, 2006	
	용수 시스템				Water for Pharmaceutical Use, Annex 3, TRS No. 929, 2005	
	아이솔레이터			Recommendation: Isolators used for Aseptic Processing and Sterility Testing		

카테고리	세부 주제	FDA	EMA	PIC/S	WHO	ICH
3. 품질 관리	OOS	Investigating Out of Specification(OOS) Test Results for Pharmaceutical Production				
	규격/시험 방법					Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A Decision Trees Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
	포장 자재	Container Closure Systems for Packaging Human Drugs and Biologics			Guidelines on Packaging for Pharmaceutical Products, Annex 9, TRS No. 902, 2002	
	검체 채취 (원자재, 제품)		GMP Guide Annex 8: Sampling of Starting and Packaging Materials	GMP Guide Annex 8: Sampling of Starting and Packaging Materials	Sampling of Pharmaceutical Products and Related Materials, Annex 4, TRS No. 929, 2005	
	불순물					Q3A(R2) Impurities in New Drug Substances Q3B(R2) Impurities in New Drug Products Q3C(R3) Impurities: Guideline for Residual Solvents
	보관품		GMP Guide Annex 19: Reference and Retention Samples	GMP Guide Annex 19: Reference and Retention Samples		
	무균 시험			Recommendation: Sterility Testing		
	안정성	Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products			Guidelines for Stability Testing of Pharmaceutical Products Containing Well Established Drug Substances in Conventional Dosage Forms, Annex 5, TRS No. 863, 1996	Q1A(R2) Stability Testing of New Drug Substances and Products Q1B Stability Testing: Photostability Testing of New Drug Substances and Products Q1C Stability Testing for New Dosage Forms Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products Q1E Evaluation of Stability Data Q5C Stability Testing of Biotechnological/Biological Products
	Parametric Release		GMP Guide Annex 17: Parametric Release	GMP Guide Annex 17: Parametric Release Recommendation: Guidance on Parametric Release		

카테고리	세부 주제	FDA	EMA	PIC/S	WHO	ICH
4. 밸리 데이션	공통	Guideline on General Principle of Process Validation	GMP Guide Annex 15: Qualification and Validation	GMP Guide Annex 15: Qualification and Validation Recommendation: Validation Master Plan, Installation and Operational Qualification, Non-sterile Process Validation, Cleaning Validation	Validation, Annex 4, TRS No. 937, 2006	
	시설설비 적격성평가				Validation – Appendix 6, Annex 4, TRS No. 937, 2006	
	HVAC 시스템				Validation – Appendix 1, Annex 4, TRS No. 937, 2006	
	용수 시스템				Validation – Appendix 2, Annex 4, TRS No. 937, 2006	
	컴퓨터화 시스템	General Principles of Software Validation Guide to Inspections of Computerized Systems in Drug Processing* Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application	GMP Guide Annex 11: Computerized Systems	GMP Guide Annex 11: Computerized Systems Good Practices for Computerized Systems in Regulated "GXP" Environments	Validation – Appendix 5, Annex 4, TRS No. 937, 2006	
	분석 방법	Analytical Procedures and Methods Validation (Draft) Bioanalytical Method Validation Reviewer Guidance: Validation of Chromatographic Method Validation of LAL Test			Validation – Appendix 4, Annex 4, TRS No. 937, 2006	Q2(R1) Validation of Analytical Procedures: Text and Methodology
	세척	Guide to Inspections of Validation of Cleaning Processes*		Recommendation: Validation Master Plan, Installation and Operational Qualification, Non-sterile Process Validation, Cleaning Validation*	Validation – Appendix 3, Annex 4, TRS No. 937, 2006	
	비무균 공정			Recommendation: Validation Master Plan, Installation and Operational Qualification, Non-sterile Process Validation, Cleaning Validation*	Validation – Appendix 7, Annex 4, TRS No. 937, 2006	
	무균 공정	Guidance for Industry: for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products		Recommendation: Validation of Aseptic Processes		

카테고리	세부 주제	FDA	EMA	PIC/S	WHO	ICH
5. GMP 실사	해외 업체 실사	Guide to Inspections of Foreign Pharmaceutical Manufacturers				
	제품 허가 승인 단계 실사(PAI)	CPGM 7346.832: Pre-Approval Inspection			Guidelines on Pre-Approval Inspection, Annex 7, TRS No. 902, 2002	
	제품 허가 승인 이후 실사	CPGM 7346.843: Post-Approval Inspection				
	실사 보고서			SOP: PIC/S Inspection Report Format	Inspection Report, Annex 6, TRS No. 908, 2003	
	임상 의약품			Aide-Memoire: GMP Particularities in the Manufacture of Medicinal Products to be used in Clinical Trials on Human Subjects		
	원료 업체	Guide to Inspections of Bulk Pharmaceutical Chemicals Guide to Inspections of Sterile Drug Substance Manufacturers CPGM 7356.002F: Active Pharmaceutical Ingredient (API) Process Inspection				
	완제 업체	Guide to Inspections of Dosage Form Drug Manufacturer's: CGMPR's CPGM 7356.002: Drug Manufacturing Inspection				
	무균 제제	CPGM 7356.002A: Sterile Drug Process Inspection				
	내용 고형제	Guide to Inspections of Oral Solid Dosage Forms Pre/Post Approval Issues for Development & Validation				
	국소 제제	Guide to Inspections of Topical Drug Products				
	내용 액제/ 현탁제	Guide to Inspections of Oral Solutions and Suspensions				
	유틸리티	Guide to Inspections of High Purity Water Systems		Aide-Memoire: Inspection of Utilities		
	동결건조	Guide to Inspections of Lyophilization of Parenterals				
	세척 공정 밸리데이션	Guide to Inspections of Validation of Cleaning Processes				
	컴퓨터화 시스템	Guide to Inspections of Computerized Systems in Drug Processing				
	QC	Guide to Inspections of Pharmaceutical Quality Control Laboratories Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories		Aide-Memoire: Inspection of Pharmaceutical QC Laboratories		
6. 기타	이온화 방사선 조사		GMP Guide Annex 12: Use of Ionising Radiation in the Manufacture of Medicinal Products	GMP Guide Annex 12: Use of Ionising Radiation in the Manufacture of Medicinal Products		

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PART I EU GMP 가이드라인



EU GMP

- EU GMP는 3개 파트와 1개의 Annex로 구성되어 있으며 EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines에 가이드라인들이 정리되어 있다.
- Volume 4는 사람과 동물 사용의 의약품 규제에 관한 사항을 Commission Directives 91/356/EEC(as amended by Directive 2003/94/EC, and 91/412/EEC respectively)에 따라서 적용하고 있다.

■ Part I – Basic Requirements for Medicinal Products

- Chapter 1 Quality Management (revision February 2008)
- Chapter 2 Personnel
- Chapter 3 Premise and Equipment
- Chapter 4 Documentation (Revision January 2011) - Coming into operation by 30 June 2011
- Chapter 5 Production
- Chapter 6 Quality Control
- Chapter 7 Contract Manufacture and Analysis
- Chapter 8 Complaints and Product Recall
- Chapter 9 Self Inspection

■ Part II

- Basic Requirements for Active Substances used as Starting Materials

■ Part III – GMP related documents

- Site Master File
- Q9 Quality Risk Management
- Q10 Note for Guidance on Pharmaceutical Quality System
- MRA Batch Certificate

■ Annexes

- Annex 1. Manufacture of Sterile Medicinal Products
- Annex 2. Manufacture of Biological Medicinal Products for Human Use
- Annex 3. Manufacture of Radiopharmaceuticals
- Annex 4. Manufacture of Veterinary Medicinal Products other than Immunological Veterinary Medicinal Products
- Annex 5. Manufacture of Immunological Veterinary Medicinal Products
- Annex 6. Manufacture of Medicinal Gases
- Annex 7. Manufacture of Herbal Medicinal Products
- Annex 8. Sampling of Starting and Packaging Materials
- Annex 9. Manufacture of Liquids, Creams and Ointments
- Annex 10. Manufacture of Pressurised Metered Dose Aerosol Preparations for Inhalation
- Annex 11. Computerised Systems (revision January 2011)
- Annex 12. Use of Ionising Radiation in the Manufacture of Medicinal Products
- Annex 13. Manufacture of Investigational Medicinal Products

- Annex 14. Manufacture of Products derived from Human Blood or Human Plasma(May 2011)
- Annex 15. Qualification and validation
- Annex 16. Certification by a Qualified person and Batch Release
- Annex 17. Parametric Release
- Annex 19. Reference and Retention Samples
- Glossary

1

EU GMP 가이드라인

Chapter 1. Quality Management System에 대한 설문조사 발표

2009년 12월 18일, ECA에서는 의약품 EU GMP 가이드라인 품질관리시스템 (Quality Management System)에 회원들을 대상으로 설문조사를 실시하였다.

설문내용에는 변화의 타당성, 기업/활동, 품질시스템, 통계학적 방법의 사용, 실사 경험과 향후 전망 등이 포함되었다.

초안에 제시된 변화의 타당성에 대한 질문에서는 설문에 참가한 197개 업체 중 67% 이상이 중요하거나 매우 중요하다고 답했으며, 3분의 1 이상의 업체가 이미 새로 도입된 품질관리시스템을 전부 또는 일부분 시행하고 있다고 밝혔으며 나머지도 곧 가이드라인에 따를 것이라고 응답하였다.

특히, PQR(제품품질심사, Product Quality Review) 또는 CAPA(교정 및 예방활동, Corrective Action & Preventive Action)처럼 최근에 도입된 GMP의 개념을 반영하는 요소들에 대해서도 대부분의 기업들이 이미 시행하고 있다고 응답하였으며, 지식경영, 지속적인 공정 개선과 위험관리시스템 등과 같은 몇몇 요구사항들은 시행을 촉진하기 위한 추가적인 해설이 필요하다고 답했다.

※ EudraLex - Volume 4 Good Manufacturing Practice Guidelines
Chapter 1 : Quality Management (p.67)

2 EU GMP 가이드라인 Chapter 5. Production 발간

2010년 11월, EU GMP 가이드라인 Chapter 5. Production의 초안이 발간되었다. 개정된 항목 5.25, 5.26, 5.27은 몇 가지 새로운 제안을 하고 있으며, 출발 물질(starting material) 공급자 자격과 GMP에 관련된 생산 활동 전반에 걸친 법적 의무에 대해 설명하고 있다. 새로운 항목인 5.31은 출발 물질 검사에 대한 설명(clarification)과 조화(harmonization)에 관한 내용을 담고 있다.

개정된 Chapter 5의 내용 중 가장 중요한 내용은 아래와 같다.

- 5.25 : 기존의 5.26 항목에 제시되어있는 “제조업자, 수입업자, 배급업자”에 대한 내용을 추가하여 설명하고 있다. 이러한 내용은 전반적인 활동 상황에 맞추고 있으며, 아직까지 미흡한 부분이 남아있다.
- 5.26 : 공급자의 승인 및 자격, 선택은 앞으로 중요한 활동이다. 출발 물질의 공급망에 수반되는 위험을 포함할 것이며, 평가를 위한 절차, 구매, 출발 물질 승인 절차에 대해 새로운 내용을 알려줄 것이다. 또한 포장재료로서 부적합한 재료는 품질평가 시스템에 반드시 문서화되어야 한다.
- 5.27 : 운반 상황에 관련된 공급망의 traceability에 관한 문서를 요구하고 있다.
- 5.31 : 이번 개정을 통해 새롭게 소개되었다. 5.31은 출발 물질 검사 시 외주에 필요한 최소한의 조건을 말하고 있다(의약품 제조업체(공급자)가 출발 물질 제조업체(피공급자)를 승인하는 조건). 정식 협의는 두 당사자간의 서명이 필요하며, 각각의 책임에 대해 특별한 주의가 요구된다. 운송 이후라도 제품 검사 시 문제가 발생되면 외주를 받은 출발 물질 제조업체는 문제에 대한 책임을 이행해야 한다.

※ EudraLex - Volume 4 Good Manufacturing Practice Guidelines
Chapter 5 : Production (p.73)

3 EU GMP 가이드라인 Chapter 6. Quality Control 개정

2010년 10월 12일, EMA는 EU GMP 가이드라인 Chapter 7 ‘품질 관리’ 개정에 관련된 Concept Paper를 발간하였다.

GMP 실시자는 분석 방법을 양도·이전하는 과정에서 시험방법 밸리데이션 부족으로 인하여 기준이탈(시험 결과가 미리 정한 합격범위를 벗어난 경우)이 발생할 수 있음을 주의해야 한다. 또한 이러한 상황은 품질관리 실험실에 대한 계약이 성립되거나 실험 시 빈번하게 발생한다.

새로운 가이드라인은 각 기업과 나라들 사이의 기술이전이 원활히 이루어질 수 있도록 명확한 정의를 제공하고, 제조 활동의 세계적인 상황 및 QbD와 같은 새로운 개념의 발전에 이바지할 것으로 생각된다.

Chapter 6 개정 과정은 다음 규정 내에서 고려되어야 한다.

- 현재 시행되고 있는 Annex16, 19, 20
- ICH Q8, Q9, Q10문서
- ICH Q11초안 문서
- 현재 진행되고 있는 Chapter 4, 7 및 Annex11
- 원료의약품 확인 상황 및 Process Analytical Technology(PAT)에 대한 Near Infrared Spectroscopy (NIR)와 같은 새로운 기술개발 Endotoxin과 Microbiological testing에 대한 고찰 역시 명확한 가이드라인이 필요하다.

※ Concept Paper on the Revision of Chapter 6 of the EU GMP Guide Quality Control (p.82)

4 EU GMP 가이드라인 Chapter 7. Outsourced Activities 개정

2010년 11월 9일, EU는 EU GMP Guide chapter 7 ‘계약 생산 및 분석’에 대한 수정사항을 게재하였다.

ICH Q10(계약품질시스템)에 명시된 내용 ‘계약 생산 및 분석’을 바탕으로 ‘외주 제작 활동’과 관련된 chapter 7이 수정되었다. 이러한 변화를 통해 기존 가이드라인의 일부 구절뿐 아니라 chapter 제목 역시 ‘계약 생산 및 분석’에서 ‘외주 제작 활동’으로 변경되었다.

개정된 chapter 7의 조항 중 가장 중요한 변화는 아래의 내용과 같다.

■ 위탁업체

- 품질시스템의 일부분인 외주 제작 활동의 관리와 검토는 책임을 요하는 중요한 부분이다. 계약을 제안한 쪽은 관리를 확실히 할 수 있도록 책임을 져야 하며, 품질 위해 관리를 구체적으로 이행해야 한다.
- 외주 제작 활동이 이루어지기 전에, 계약을 제안한 쪽은 계약을 체결하는 업체 쪽의 GMP 수준을 평가해야 한다. 특히, 계약을 제안하는 쪽은 공급업체에 적용되는 GMP뿐만 아니라 계약을 받아들이는 쪽의 협력업체에 적용되는 GMP 수준 역시 적절하도록 해야 한다.

■ 수탁업체

- 하청업자를 평가할 수 있는 자료는 계약을 제안하는 쪽과 받아들이는 쪽 사이에서 동등하게 이용 가능하다.
- 계약을 받아들이는 업체는 계약을 제안한 업체가 실행하는 외주활동에 부정적 영향을 미쳐서는 안된다.

■ 계약과 관련된 정보

- 외주활동과 관련된 의사소통이 확실히 이루어져야 하고, 서로 책임감을 가져야 한다.
- 계약을 체결할 때 외주활동의 각 과정(정보 관리, 기술전수, 공급망, 하청업자와의 계약, 구매한 원료 물질의 품질, 품질 관리하는데 필요한 분석과 샘플링)에 대해 책임질 수 있는 사람을 명확히 정해야 한다.
- 외주활동과 관련되어 기록된 정보들은 계약을 제안한 쪽이 열람 가능해야 하며 보관 유지되어야 한다.
- 계약이 체결되면 계약을 제안한 쪽이 계약을 받아들이는 쪽과 하청업자를 점검할 수 있다.

결론적으로 chapter 7은 계약을 제안한 위탁업체에게 계약을 받아들이는 수탁업체를 관리할 수 있는 지침을 제공하고 있다.

※ EudraLex - Volume 4 Volume 4 Good Manufacturing Practice Guidelines
Chapter 7: Outsourced Activities (p.86)

5 EU GMP 가이드라인 Annex 11 및 Chapter 4 개정

2011년 1월, EU GMP Annex 11 ‘자동화 시스템’ 및 Chapter 4 ‘문서화’의 개정판이 발간되었다.

이 개정판은 FDA 규정 Part 11 ‘전자기록 및 전자서명’과 동등한 영향력을 가진다.

아래 내용은 주요 변경사항을 요약한 것이다.

■ Annex 11의 변경 사항 : Annex 11의 범위 확대

- Annex 11은 GMP 규제 분야에서 사용되는 모든 자동화 시스템에 적용된다. 이의 범위는 매우 광범위하며, 내부개발 문서 등 모든 데이터베이스 자동화 시스템을 포함한다.
- Annex 11의 적용은 검증이 이루어져야 한다. 즉, IT 기술이 확보되어야 한다. 어떤 규정이든지 처음에 IT기반 적격성 평가가 필수적으로 요구된다.
- 자동화 시스템이 공정 매뉴얼을 대체해도 의약품 품질·공정 관리 및 품질보증에 저하되지는 않을 것이다.

또한 Annex 11 개정판의 범위 확대는 다음 분야에도 영향을 미친다.

- System life cycle을 통한 위험관리
- 새로운 역할 및 책임
- 공급자와 서비스 제공자
- 밸리데이션
- 데이터 완전성 관리
- 전자서명
- 검증된 시스템의 IT 지원
- Maintaining validation

■ Chapter 4 ‘문서화’

EU GMP 가이드라인 Chapter 4 ‘문서화’의 개정판은 Annex 11과 동시에 발간되어 2011년 6월 30일부터 효력을 나타낼 것이다. 그 결과 전자문서의 이용 증가로 기존의 문서 작성, 관리 및 보관에 변화를 초래하게 될 것이다. 더욱이 문서는 서류, 컴퓨터 파일, 사진 매체 등 다양한 형태로 관리될 수 있다. 이것은 21 CFR 11에 정의된 ‘전자기록 및 전자서명’의 내용과 유사하다.

EU 규정담당자는 앞으로 예상되는 GMP 문서형태에 대해 FDA보다 세부적으로 설명하였다. 따라서 이번 개정판은 새로운 규정을 이해하고 실행하는데 도움을 줄 것이다.

※ The New GMP Annex 11 and Chapter 4 is Europe's Answer to Part 11 (p.90)

6 EU GMP 가이드라인 Part 3 발간

2011년 1월 31일, EMA는 EU GMP Guide Part 3로 ICH Q9과 Q10을 채택했다.

■ 제약품질시스템(ICH Q10)

ICH Q10은 제품의 lifecycle을 위해 고안된 제약품질시스템의 정보를 제공하기 때문에 cGMP를 준수할 때 많은 도움을 준다. 이러한 ICH Q10을 이행할 때 활용되는 개념과 용어를 정리하기 위해서 EU는 GMP Guide chapter1, 2, 7의 최신화가 필요하다는 것을 알게 되었다.

GMP를 적용하는데 있어 ICH Q10 내용들이 선택사항일 수 있지만, 이 내용을 반영한다면 의약품개발과 제조활동의 연관성을 강화시킬 수 있다.

■ 품질위험관리(ICH Q9)

품질위험관리는 제조환경뿐만 아니라 의약품 개발과 시판허가서류의 품질 부분을 준비하는데 적용할 수 있다.

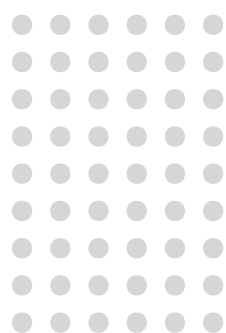
또한 이 지침은 규제기관에서 시판허가서류의 품질평가, GMP 실사, 의심되는 품질 결함을 다룰 때에도 적용된다.

이 내용은 2008년 3월 Annex 20으로 GMP Guide에 포함되었다. 그리고 GMP Guide Part 3이 만들어짐에 따라 Part 3 위치에 넣는 것이 더 적절하다고 판단되었다.

이번 수정안에는 품질위험관리의 원칙들이 포함되었다. 그리고 이전 Annex 20의 내용은 선택사항으로 품질위험관리의 절차와 적용의 예시를 제공한다.

※ Pharmaceutical Quality System (ICH Q10) (p.95),
Quality Risk Management (ICH Q9) (p.113)

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PART II

WHO

가이드라인



WHO GMP

- WHO GMP는 4개 파트 : WHO good manufacturing practices, Risk analysis, Technology transfer, Training materials 로 구성되어 있다.

■ WHO good manufacturing practices

- Quality assurance of pharmaceuticals: a compendium of guidelines and related materials
- WHO good manufacturing practices: main principles for pharmaceutical products. Annex 3, WHO Technical Report Series 961, 2011
- Frequently Asked Questions: Good Manufacturing Practice (GMP) in Pharmaceutical Practice
- Active pharmaceutical ingredients (bulk drug substances). Annex 2, WHO Technical Report Series 957, 2010
- Pharmaceutical excipients. Annex 5, WHO Technical Report Series 885, 1999
- WHO good manufacturing practices for sterile pharmaceutical products. Annex 6, WHO Technical Report Series 961, 2011
- Biological products. Annex 3, WHO Technical Report Series 834, 1993
- WHO good manufacturing practices for blood establishments (jointly with the Expert Committee on Biological Standardization). Annex 4, WHO Technical Report Series 961, 2011
- Pharmaceutical products containing hazardous substances. Annex 3 WHO Technical Report Series 957, 2010

- Investigational pharmaceutical products for clinical trials in humans. Annex 7, WHO Technical Report Series 863, 1996
- Herbal medicinal products. Annex 3, WHO Technical Report Series 937, 2006
- Radiopharmaceutical products. Annex 3, WHO Technical Report Series 908, 2003
- Water for pharmaceutical use. Annex 3, WHO Technical Report Series 929, 2005
- WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. Annex 5, WHO Technical Report Series 961, 2011
- Validation. Annex 4, WHO Technical Report Series 937, 2006

■ Risk analysis

- Application of Hazard Analysis and Critical Control Point (HACCP) Methodology in Pharmaceuticals. Annex 7, WHO Technical Report Series 908, 2003

■ Technology transfer

- WHO guidelines on transfer of technology in pharmaceutical manufacturing. Annex 7, WHO Technical Report Series 961, 2011

■ Training materials

- WHO Basic Training Modules on GMP(Includes an introduction, resource and study pack for trainers)
- WHO supplementary training modules on GMP(Includes drafts of GMP for Validation, Water, and Air Handling Systems)

1 WHO, Annex 2 ‘API에 대한 GMP’ 가이드라인 개정

2010년 개정 발간된 WHO의 기술문서시리즈(TRS)를 살펴보면 ‘원료의약품에 대한 GMP’를 비롯한 많은 수의 Annex가 개정되었다.

WHO의 ‘원료의약품에 대한 GMP’ 규정인 Annex 2는 ICH Guideline Q7과 동일한 내용으로 이루어져 있는데, 명확히 할 필요가 있다고 여겨지는 다음과 같은 문제들이 언급되어 있다.

- API(Active Pharmaceutical Ingredients)출발 물질에 대한 정의
- 품질관리시스템의 소개 중 관리의 역할
- 생산현장에서의 권한위임
- 주요 물질의 제한된 공급자에 대한 시스템
- 수령 전/후 컨테이너 또는 컨테이너 그룹에 대한 실험
- 배치정보
- 보유 샘플

또한 WHO에서는 뒷부분에 출발 물질에 반드시 다음 사항을 언급하도록 규정하고 있다.

- ✓ 물질 및 순도에 대한 충분한 정의
- ✓ API 합성 초기 전구체 및 합성 단계에 대한 설명
- ✓ 충분히 밝혀진 구조와 함께 분리·정제된 물질
- ✓ 유효성과 불순물에 대한 확인 및 한도 시험과 같은 한 개 이상의 특징적인 확인시험에 대한 명확한 정의

※ WHO Technical Report Series 957

Annex 2. WHO good manufacturing practices for active pharmaceutical ingredients
(출처 명시로 첨부 생략 http://whqlibdoc.who.int/trs/WHO_TRS_957_eng.pdf#page=144)

2

WHO, Annex 3

‘위험물질을 포함하는 의약품’ GMP 가이드라인 발간

2010년 7월, WHO에서는 Annex 3 ‘위험물질을 포함하는 의약품’ GMP 가이드를 발간하였다.

가이드에서는 위험물질에 대해 밀폐된 시스템에서 다룰 것을 권고하고 있으며, 제조 시에도 출입구 또는 공조시스템 등과 같이 설비가 분리되어 있는 전용 설비를 사용할 것을 권장한다. 이때, 설비가 어느 정도 분리되어야 하는가에 대한 질문에 대해서는 위험평가(risk assessment)에 근거하여 설명되어 있는데, 이 평가는 환경과 인체에 여러 단계의 위험성이 야기될 수 있는 각 제조공정간의 차이를 충분히 고려하여야 한다.

중앙공조시스템이 사용되는 환경에서 혼입되는 공기는 가급적 작업자와 가까운 위치에서 H13필터를 반드시 통과시켜야 하며, 중앙시스템에 문제가 발생하는 경우를 대비해 5분 이상 공급이 가능한 가스통 등과 같은 백업 시스템이 마련되어 있어야 한다.

HVAC 시스템에서는 당연히 외부환경으로부터 제조 구역에 이르기까지 단계적인 음압을 유지할 것을 요구하고 있다.

압력의 변동이 있는 경우에는 경보 장치가 울리고, 전원이 켜지는 순간부터 꺼지는 순간까지 음압을 유지하며, 작업실 별 압력 상태를 각각 표시할 수 있도록 시스템을 설정하여야만 한다.

되돌아오거나 순환된 공기에 대한 재사용 여부는 위험평가에 근거해 결정하도록 하며, 에너지재생 시스템의 사용은 공기 누출 위험이나 공급 및 배기가스의 접촉이 없는 경우에만 허용된다.

※ WHO Technical Report Series 957

Annex 3. WHO good manufacturing practices for pharmaceutical products containing hazardous substances (p.425)

3 WHO, Annex 4 ‘무균의약품 GMP’ 초안 발간

2010년 7월, WHO에서는 Annex 4 ‘무균의약품(Sterile Pharmaceutical Products, SPP)에 대한 우수의약품 제조품질관리기준(GMP)’의 새로운 초안을 발표하였다.

WHO의 무균의약품에 대한 GMP기준은 2002년 TRS 9002문서의 Annex 6에 있었으나, 최근 관련 기술과 규정의 향상으로 개정의 필요성이 대두되었다. 따라서 이번 초안은 다음과 같은 최신 국제 규정과 조화를 이루는 방향으로 작성되었다.

- 미국 FDA 산업지침
 - 무균 공정에 의해 생산된 무균의약품
- 유럽연합 GMP 가이드라인
 - Annex 1
- 일본 산업지침
 - 무균 공정에 의해 생산된 무균의약품
- ISO14644
 - Clean rooms and Associated Controlled Environments

이번 초안은 기존 문서와 같이 유럽연합 GMP 가이드라인(Annex 1)의 구조를 반영하였고, BFS(Blow Fill Seal) 설비와 isolator에 대한 내용을 새로 추가하였다. 또한, “무균의약품의 완성(Finishing of sterile products)”에서는 마개 공정(capping)에 대한 기준, “무균의약품용 물질의 제조”에서는 ISO14644 기준이 각각 적용되었다.

특히 이번 초안의 단계적 시행은 업체의 투자비용 증가 (마개 공정 등)와 맞물려 있어 그 파급효과가 클 것으로 생각된다.

※ WHO Technical Report Series 957

Annex 4. WHO good manufacturing practices for sterile pharmaceutical products (p.442)

4 WHO, Quality Risk Management 가이드라인 초안 발간

2010년 8월, WHO는 품질위험관리(Quality Risk Management, QRM) 가이드라인 초안을 발표하였다.

Chapter 1에서는 ICH Q9에 기초하여 QRM 접근에 대해 언급하고 있는데, 이는 EU GMP 가이드라인, ICH Q8, FDA의 위험기반 접근 내용보다 더욱 구체적으로 작성되었다. 그러나 WHO는 ICH Q9에 언급된 것 이외에도 다른 방식의 위험관리 모듈이 적용될 수 있다는 사실을 강조한다.

본 가이드라인에서는 ICH Q9에서 적용되는 QRM 관련 사항들을 모두 요구하게 될 것이다. 흥미로운 사실은 WHO가 QRM의 틀 안에서 GCP와 GLP의 연결을 꺾고 있다는 사실이다.

2.2.1에는 QRM 실사 체크리스트가 담겨 있으며, 2.2.2에서는 위험 기반 판단의 실사에 대해 설명해 놓았다.

Chapter 3에서는 의약품 제조업자에 대한 QRM 요구사항을 매우 자세하게 다루고 있다. 이 Chapter에서는 교육과 훈련에 대해 설명하고 있는데, QRM 공정의 시작부터 교정조치의 확립과 QRM 내용의 확인까지 자세히 언급하고 있다. 이 Chapter의 또 다른 부분에서는 의약품의 개발 및 밸리데이션, 품질검사 동안의 QRM 적용에 대해 알려주고 있는데, 특히 공정 밸리데이션에 대해서는 동일한 주제의 FDA 초안을 인용하고 있다. 밸리데이션의 횟수 또는 적당한 배치 규모는 아직 확정되지는 않았으나, 기존의 밸리데이션 운영 시 통용되어온 3번의 횟수에서는 일탈이 발생할 수 있음을 심각하게 고려해야 한다(예: 희귀의약품 제조 밸리데이션의 경우).

Chapter 4는 위험관리 틀에 대해 다루고 있으며, 의약품 품질연구소(Product Quality Research Institute, PQRI)의 문서를 참고하여 확률 대 영향의 관계에 대해 기술되어 있다. 이 관계는 위험 상황을 상, 중, 하의 세 단계로 분류할 수 있도록

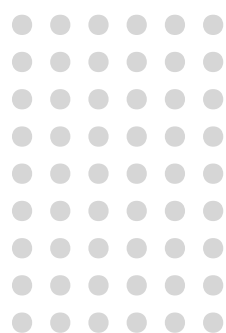
도와줄 것이며, QRM 팀은 각각의 단계에 대해 정의 내릴 수 있을 것이다. 유용한 툴로서는, 결과 테이블이 실려 있는데, 확률과 영향의 분류에 대한 사례도 함께 제공하고 있다.

Chapter 5는 용어에 대한 부분을 다루고 있는데, 주로 다른 Chapter의 내용을 보완해준다. 이 Chapter의 주된 특징은 QRM 분야에 대해 MHRA에서 다뤄진 Q&A와 관계된 내용들이다. 어떤 구절은 그대로 인용되기도 하였으며, MHRA와 같이 본 가이드라인에서도 위험기록문서(Risk Register)를 요구하고 있다.

이번 WHO의 가이드라인 초안은 놀랄만큼 자세하게 작성되어 있으며, 공식적인 실사 체계 안에서의 QRM 준비 과정에 대한 방향을 제공해줄 것이다. 이와 함께 QRM을 개시하기 위한 지침서가 되어줄 것이다. 하지만, 신흥국가와 같은 곳의 제약업체에서 QRM을 꼼꼼하게 적용하는 데에는 시간이 걸릴 것으로 판단된다.

※ WHO GUIDELINE ON QUALITY RISK MANAGEMENT (p.468)

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PART Ⅲ EMA 가이드라인



EMA GMP

- EMA GMP는 10개의 파트로 구성되어 각각의 가이드라인이 정리되어 있다.

- ☐ Active Substance Manufacturing
- ☐ Impurities Specifications
- ☐ analytical procedures and analytical validation
- ☐ Excipients
- ☐ Packaging
- ☐ Stability
- ☐ Pharmaceutical development
- ☐ Specific types of products
- ☐ Post approval change management protocols
- ☐ Herbal medicinal products.

☐ Active substance

- Q 11 Development and manufacture of drug substances (chemical entities and biotechnological / biological entities), Step 3 (Draft guideline, Release for consultation May 2011)
- Template for the Qualified Person's declaration concerning GMP compliance of the active substance used as starting material and verification of its supply chain "The QP declaration template" (Draft template, Release for consultation Dec 2010)

- Active Substance Master File Procedure. (Draft guideline, Release for consultation Apr 2006)
- Summary of Requirements for Active Substances in the Quality Part of the Dossier (Draft guideline, 1 Jun 2004)
- Active Substance Master File Procedure (Adopted guideline, 1 Apr 2005)
- Chemistry of New Active Substances (Adopted guideline, 1 Dec 2003)
- Investigation of Chiral Active Substances (Adopted guideline, Oct 1993)
- Chemistry of Active Substances (Adopted guideline, Oct 1987)

■ Manufacturing

- Process Validation (Adopted guideline, Feb 2001)
- Process Validation (Concept paper, Feb 2010)
- Annex II: Process Validation - Non-Standard Processes (Adopted guideline, Jul 2004)
- Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products (Adopted guideline, Mar 2001)
- Manufacture of the Finished Dosage Form (Adopted guideline, Sep 1995)
- Annex: Start of Shelf-Life of the Finished Dosage Form (Adopted guideline, May 2001)
- The use of Ionizing Radiation in the Manufacture of Medicinal Products (Adopted guideline, Dec 1991)

■ Impurities

- Specification Limits for Residues of Metal Catalysts (Adopted guideline, Feb 2008)

- Limits of genotoxic impurities (Adopted guideline, Jun 2006)
- Control of Impurities of Pharmacopoeial Substances (Adopted guideline, Dec 2003)
- Impurities in New Medicinal Products (ICH Q3B (R2)) (Adopted guideline, Feb 2003)
- Impurities Testing: Impurities in New Drug Substances (ICH Q3A R2)) (Adopted guideline, Feb 2002)
- Impurities: Residual Solvents (ICH Q3C (R4)) (Adopted guideline, Sep 1997)
- Impurities: Guideline for residual solvents (ICH Topic Q3C (R5)) (Adopted guideline, Mar 2011)
- Annexes to Specifications for class 1 and class 2 residual solvents in active substances (Adopted guideline, Jul 2004)

■ Specifications, analytical procedures and analytical validation

- ICH Topic Q8, Q9 and Q10 Quality Implementation Working Group Questions and Answers (Adopted guideline, Dec 2009)
- Q 4B Annex 11 Capillary Electrophoresis General Chapter (Draft guideline, Release for consultation Dec 2009)
- Q 4B Annex 12 Analytical Sieving General Chapter (Draft guideline, Release for consultation Dec 2009)
- Q 4B Annex 9 Step 3 Tablet Friability General Chapter (Draft guideline, Release for consultation Jun 2009)
- Q 4B Annex 10 Step 3 Polyacrylamide Gel Electrophoresis (Adopted guideline, Dec 2009)

- Q 4B Annex 8 to Note for evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on sterility test general chapter (Adopted guideline, Jun 2009)
- Q 4B Annex 7 Dissolution test general chapter (Adopted guideline, Dec 2009)
- Setting specifications for related impurities in antibiotics (Concept paper, Release for consultation Jun 2010)
- Q 4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions (Adopted guideline, Dec 2007)
- Q 4B Annex 1 to Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Residue on Ignition/Sulphated Ash General Chapter (Adopted guideline, Dec 2007) · Q 4B Annex 2 to Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Test for Extractable Volume in Parenteral Preparations General Chapter (Adopted guideline, Jun 2008)
- Q 4B Annex 3 to Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Test for Particulate Contamination: Sub-Visible Particles General Chapter (Adopted guideline, Jun 2008)
- Q 4B Annex 4A to Evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on microbiological examination of non-sterile products: microbiological enumeration tests (Adopted guideline, Release for consultation Jun 2008)
- Q 4B Annex 4B to Evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on test for microbiological examination of non-sterile products: tests for specified micro-organisms (Adopted guideline, Release for consultation Jun 2008)

- Q 4B Annex 4C to Evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on test for micrological examination of non-sterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use (Adopted guideline, Release for consultation Jun 2008)
- Q 4B Annex 5 to Evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on disintegration test general chapter (Adopted guideline, Jun 2009)
- Use of Near Infrared Spectroscopy (NIRS) by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations revision 1 (Draft guideline, Release for consultation Feb 2009)
- Use of Near Infrared Spectroscopy (NIRS) by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations (Adopted guideline, Feb 2003)
- Real Time Release Testing Draft guideline (Concept paper, Mar 2010)
- Parametric Release (Adopted guideline, Feb 2001)
- Q 6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (Adopted guideline, Nov 1999)
- Q 2(R1) Validation of Analytical Procedures: Text and Methodology (Adopted guideline, Nov 1994 (Part I), Dec 1996 (Part II) Jun 1995 (Part I), Jun 1997 (Part II) Combines former ICH Q2A (Definitions and Terminology) and ICH Q2B (Methodology) guidelines Specifications and control Tests on the Finished Product Adopted guideline 3AQ11A Dec 1991)

■ Excipients

- Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (Adopted guideline, Jul 2007)
- Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (Draft guideline, Release for consultation Feb 2003)
- Excipients in the label and package leaflet of medicinal products for human use (Adopted guideline, Jul 2003)
- Quality of Water for Pharmaceutical Use (Adopted guideline, May 2002)
- Reflection Paper on Water for Injection prepared by Reverse Osmosis (Adopted guideline, Mar 2008)
- Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products (Adopted guideline, Jul 1997)
- Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (Adopted guideline, Feb 1994)

■ Packaging

- Plastic Primary Packaging Materials (Adopted guideline, May 2005)

■ Stability

- Stability testing for applications for variations to a marketing authorisation (Draft guideline, Released for consultation Jul 2011)
- Stability Testing for Applications for Variations to a Marketing Authorisation (Adopted guideline. May 2005)
- Stability Testing of New Drug Substances and Drug Products (ICH Q1A (R2)). (Adopted guideline, Feb 2003)

- Stability Testing of Existing Active Ingredients and Related Finished Products. (Adopted guideline, Dec 2003)
- Annex: Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances (Adopted guideline, Apr 2003)
- Evaluation of Stability Data (ICH Q1E) (Adopted guideline, Feb 2003)
- Stability Data Package for Registration in Climatic Zones III and IV (ICH Q1F) (Adopted guideline, Feb 2003)
- Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products (ICH Q1D) (Adopted guideline, Feb 2002)
- In-Use Stability Testing of Human Medicinal Products (Adopted guideline, Feb 2001)
- Maximum Shelf-Life for Sterile Products for Human Use after first opening or following Reconstitution (Adopted guideline, Jan 1998)
- Photostability Testing of New Active Substances and Medicinal Products (ICH Q1B) (Adopted guideline, Dec 1996)
- Stability Testing: Requirements for New Dosage Forms (ICH Q1C) (Adopted guideline, Dec 1996)

■ Pharmaceutical development

- Pharmaceutical Development of Medicines for Paediatric Use (Draft guideline, Release for consultation May 2011)
- Pharmaceutical Development (ICH Q8 (R2)) (Adopted guideline, Nov 2005)
- Annex to Development Pharmaceuticals: Decision trees for selection of sterilisation methods (Adopted guideline, Feb 1999)
- Development Pharmaceuticals (Adopted guideline, Jan 1998)

■ Specific types of products

- Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (non-polymeric surfactants) (Draft reflection paper, Release for consultation Sep 2010)
- Concept paper on the revision of the guideline on radiopharmaceuticals based on monoclonal antibodies (Concept paper, Release for consultation Sep 2009)
- Radiopharmaceuticals Overview of comments (Adopted guideline, Nov 2008)
- Radiopharmaceuticals (Adopted guideline, Dec 1990)
- Medicinal Gases: Pharmaceutical Documentation (including recommendation on non-clinical safety requirements for well established medicinal gases) (Adopted guideline, Jan 2002)
- Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials (Adopted guideline, Mar 2006)
- Pharmaceutical Quality of Inhalation and Nasal Products (Adopted guideline, Apr 2006)
- Suitability of the Graduation of Delivery Devices for Liquid Dosage Forms (Draft guideline, Feb 2005)
- Development of CHMP Guideline on Dosing Delivery of Injectable Liquids (Concept paper, Jun 2004)
- Quality of Modified Release Products A) Oral Solid Dosage Forms B) Transdermal Dosage Forms Section I (Quality) (Adopted guideline, Jul 1999)

- Concept paper on the revision of the note for guidance on quality of modified release oral dosage forms and transdermal dosage forms: Section I (quality) (Concept paper, Jun 2010)
- Radiopharmaceuticals Based on Monoclonal Antibodies (Adopted guideline, May 1991)

■ Post approval change management protocols

- Questions and answers on post approval change management protocols (Draft guideline, Release for consultation Oct 2010)

■ Herbal medicinal products

- Reflection paper on stability testing of herbal medicinal products and traditional herbal medicinal products Overview of comments (Adopted guideline, Nov 2010)
- Questions & answers (Q&A) on quality of herbal medicinal products/ traditional herbal medicinal products Questions and answers Nov 2010 (Adopted guideline, Jan 2011)
- Development of a guideline on preparation on herbal teas (Concept paper, Release for consultation Sep 2008)
- Markers used for quantitative and qualitative analysis of Herbal Medicinal Products and traditional Herbal Medicinal Products Overview of comments (Adopted guideline, Jul 2008)
- Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products/ Traditional Herbal Medicinal Products in the SPC Overview of comments (Adopted guideline, Apr 2010)

- Quality of Combination Herbal Medicinal Products / Traditional Herbal Medicinal Products Overview of comments (Adopted guideline, Jun 2008)
- The use of Fumigants (Adopted guideline, Oct 2006)
- Good Agricultural and Collection Practice for starting materials of Herbal Origin Overview of comments (Adopted guideline, Jul 2005)
- Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products Adopted guideline (Adopted guideline, Sep 2011)
- Test procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products (Adopted guideline, Sep 2011)

1 EMA, 운송 시 저장조건에 대한 Concept Paper 발간

2010년 10월, EMA는 운송 시 저장조건과 관련된 Concept Paper를 발간하였다.

발간 목적은 새로운 GDP(Good Distribution Practice, 유통관리기준)와 GMP 가이드언스를 만들기 위한 것이며, 명확한 저장조건 등 가이드언스를 수정할 필요성이 있음을 알리는 것이다. 현재 가이드언스는 1996년에 작성되어 2003년에 수정이 되었으나, 규제적인 측면에서 의약품과 API(Active Pharmaceutical Ingredient, 원료의약품)는 운송 도중 손상을 방지하기 위한 명확한 가이드언스가 미흡한 실정이었다. 그 동안 공급 망에서 일어나는 복잡성과 취약성의 증가로 세계 제조업에는 상당한 변화가 있었다.

새로운 가이드언스로 인한 효과는 다음과 같다.

- 의약품이 EU로 수입되는 등 운송이 증가함에 따라 제조와 분배 관련 규제가 더욱 중요해졌다.
- 열대 지역 제조공장이 증가하고, 운송시스템이 열악함에 따라 지역 내, 열대 지방과 EU간 운송 시 더 많은 고려가 있어야 한다.
- 운송 시 동결 발생 위험과 그로 인한 영향을 고려해야 한다.
- 제조와 운송단계에서도 품질위험관리의 방침이 적용되는 것이 기대된다.

※ Concept paper on storage conditions during transport (p.492)

2 EMA, ICH Q11 가이드라인 발간

2011년 6월, 의약품 성분(화학적·생물학적)의 개발 및 제조에 대한 ICH 가이드라인 Q11이 Step3 문서로 게시되어, 향후 API(Active Pharmaceutical Ingredient, 원료 의약품)의 개발 및 제조에 큰 영향을 미칠 것으로 예상된다.

가이드라인의 도입부분에는 의약품 성분의 이해 및 개발공정의 접근법과 공통기술 문서(Common Technical Document, CTD) 섹션 3.2.S.2.2-3.2.S.2.6에 제공된 정보가 정의되어 있다. 또한, 의약품 성분의 개발 및 제조와 관련하여, 의약품개발(Q8), 품질위험관리(Q9), 제약품질시스템(Q10)에 명시된 원리 및 개념이 자세하게 설명되어 있다.

- 약효성분 CQAs와 관련된 물질특성 및 공정변수·화학적 성분
- 공정변수의 라이프사이클 관리를 위한 품질위험관리 이용
- 생명공학제품 단위 공정을 위한 Design Space 프리젠테이션
- 적절한 출발 물질 선택
- 선택된 CQAs를 위한 관리 요소 요약

※ ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/biological entities) Step 3 (p.496)

3

EMA, BT기술 유래 원료물질의 공정 밸리데이션에 대한 Concept Paper 발간

2011년 5월, EMA는 “BT기술 유래 원료물질의 의약품 공정 밸리데이션 가이드라인 필요성에 관한 Concept Paper”를 발간했다.

ICH를 통해 협의된 기존의 문서가 있긴 하지만, BT기술 유래 제품에 대한 평가 및 밸리데이션 이외의 구체적 가이드라인이 존재하지 않았기 때문에 가이드라인의 개발 필요성이 부각되었다.

물론 ICH Q5와 Q11(초안) 가이드라인이 BT기술 유래 원료물질의 평가 및 밸리데이션과 관련된 중요한 사항을 다루고 있지만, “DNA 또는 숙주 세포 단백질의 불순물 정제, column 및 막 살균, 평균수명, 보류시간, 재가공, 중간체의 pooling, 평가 및 밸리데이션 연구에 포함될 필요가 있는 batch 선택과 같은 사항”과 같은 내용을 자세히 다루고 있지는 않다. 이러한 사항들은 제조공정과 결과물을 이해하는데 필수적이며, 이는 판매허가과정 동안 심사자에게도 중요한 요소이다.

※ Concept paper on the need for a guideline on process validation of medicinal products containing biotechnology derived proteins as active substance (p.513)

4 EMA, ICH Q8, Q9, Q10 Q&A 4판 발간

2010년 12월, ICH Q-IWG(Quality Implementation Working Group, 품질관리시행실무단)에서 ICH 가이드라인 Q8, Q9, Q10 Q&A 4판을 발간하였다. 이 문서는 현재 EMA 홈페이지에서 확인할 수 있다.

이 Q&A는 ICH 가이드라인 Q8, Q9, Q10을 자세히 설명하고, Design Space, RTR(Real Time Release, 실시간 출하)시험, Knowledge Management(지식경영)시행을 촉진하려는 목적으로 지난 2008년에 1판이 발간된 바 있다.

최신 개정판에서 Design Space의 outer limit는 상업적 규모의 공정 밸리데이션이 이루어지는 동안 평가되어야 하는지에 대해 언급되었다.

결론은 “상업적 규모의 공정 밸리데이션이 이루어지는 동안 Design Space의 outer limit에 대해서는 Batch 적격성 평가를 시행할 필요가 없으며, 대신 Design Space는 개발연구기간 동안 충분히 검토되어야 한다.”는 것이다.

※ ICH guideline Q8, Q9 and Q10 - questions and answers volume 4 (p,516)

5 APIC, “ICH Q7 How to do” 안내서 발간

2010년 10월, APIC는 “ICH Q7 How to do” 안내서를 발간하였다.

EU의 API 제조업체들이 중요하고 유용한 문서 중 하나로 꼽는 이 안내서는 ICH Q7 가이드라인에서 API 제조업체가 이행해야만 하는 GMP 요구사항에 대해 설명하고 있다.

저자는 “How to do”가 GMP 규정을 100% 준수하기 위한 해설서가 되기를 원하지는 않는다. 단지 API 제조소에서 ICH Q7 가이드라인이 구체적으로 답변하지 못하는 문제들을 해결해 나가는데 다양한 사례와 권고 사항들로 구성된 이 해설서가 도움이 되기를 희망하고 있다.

다음은 대표적인 개정 사항이다.

- Chapter 2에서는 GMP 준수 시 변경관리 등 각각에 대한 품질관리시스템 모니터링 등의 권고사항을 제공한다.
- Chapter 3에서는 민감한 장소(무균제제 등)에서 근무하는 직원들의 교육에 대한 요구사항과 이를 적용하기 위한 조언을 구체적으로 기술하고 있다.

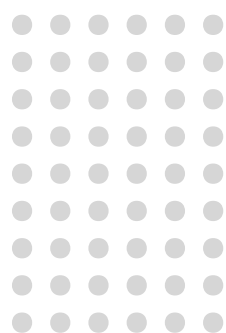
※ GMPs for APIs: “How to do” Document

Interpretation of the ICH Q7a Guide Version 6

(출처 명시로 첨부 생략)

http://apic.cefic.org/pub/How%20to%20do%20-%20ICH%20Q7a_Feb2010.pdf

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PART IV

FDA

가이드라인



FDA GMP

- FDA GMP 관련 가이드는 39개가 있다.
-
- Non-Penicillin Beta-Lactam Risk Assessment: A CGMP Framework (Draft Guidance 03/14/11)
 - Bar Code Label Requirements--Questions and Answers (Final Guidance 10/05/06)
 - COMPRESSED MEDICAL GASES GUIDELINE (Final Guidance 02/01/89)
 - Computerized Systems Used in Clinical Trials (Final Guidance 05/10/07)
 - Current Good Manufacturing Practice for Combination Products (Draft Guidance 10/04/04)
 - Current Good Manufacturing Practice for Medical Gases (Draft Guidance 05/06/03)
 - Current Good Manufacturing Practice for Phase 1 Investigational Drugs (Final Guidance 07/14/08)
 - Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products (Final Guidance 05/04/11)
 - Expiration Dating and Stability Testing of Solid Oral Dosage Form Drugs Containing Iron (Final Guidance 06/27/97)
 - Expiration Dating of Unit-Dose Repackaged Drugs: Compliance Policy Guide (Draft Guidance 05/31/05)
 - Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP_PRA(Final Guidance 01/11/06)

- Good Laboratory Practice Regulations Questions and Answers (Final Guidance 03/02/98)
- Guidance for Hospitals, Nursing Homes, and Other Health Care Facilities - FDA Public Health Advisory (Final Guidance 04/05/01)
- Investigating Out-of-Specification Test Results for Pharmaceutical Production (Final Guidance 10/11/06)
- Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients (Draft Guidance 04/17/98)
- Marketed Unapproved Drugs -- Compliance Policy Guide (Final Guidance 09/19/11)
- Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (Draft Guidance 09/29/11)
- Nuclear Pharmacy Guideline Criteria for Determining When to Register as a Drug Establishment (Final Guidance 03/02/98)
- Part 11, Electronic Records; Electronic Signatures Scope and Application (Final Guidance 09/03/03)
- PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (Final Guidance 09/29/04)
- PET Drug Products - Current Good Manufacturing Practice (CGMP) (Final Guidance 12/09/09)
- Pharmaceutical Components at Risk for Melamine Contamination (Final Guidance 08/06/09)
- Pharmacy Compounding -- Compliance Policy Guide (Final Guidance 05/01/02)

- Possible Dioxin/PCB Contamination of Drug and Biological Products (Final Guidance 08/23/99)
- Powder Blends and Finished Dosage Units - Stratified In-Process Dosage Unit Sampling and Assessment (Draft Guidance 11/07/03)
- Powder Blends and Finished Dosage Units - Stratified In-Process Dosage Unit Sampling and Assessment: Revised Attachments (Draft Guidance 11/01/03)
- Preparation of Investigational New Drug Products (Human and Animal) (Final Guidance 11/01/92)
- Prescription Drug Marketing Act? Donation of Prescription Drug Samples to Free Clinics (Final Guidance 03/01/06)
- Prescription Drug Marketing Act (PDMA) Requirements- Questions and Answers (Final Guidance 11/13/06)
- Process Validation: General Principles and Practices (FINAL Guidance 01/24/11)
- Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations (Final Guidance 09/27/06)
- Questions and Answers on Current Good Manufacturing Practices (CGMP) for Drugs (Final Guidance 03/25/11)
- Review of FDA's Implementation of the Drug Export Amendments of 1986 (Final Guidance 11/01/89)
- Sterile Drug Products Produced by Aseptic Processing? Current Good Manufacturing Practice (Final Guidance 09/29/04)
- Street Drug Alternatives (Final Guidance 03/01/00)

- Testing of Glycerin for Diethylene Glycol (Final Guidance 05/01/07)
- The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 - Current Good Manufacturing Practice (CGMP) (Final Guidance 01/26/10)
- Current Good Manufacturing Practices (CGMPs)/Compliance and Chemistry, Manufacturing, and Controls (CMC) Comparability Protocols - Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information (Draft Guidance 09/05/03)
- Current Good Manufacturing Practices/Compliance and Small Entity Compliance Guide PET Drugs--Current Good Manufacturing Practice (CGMP); Small Entity Compliance Guide (Final Guidance 08/04/11)

1 FDA, 공정 밸리데이션 가이드선 발간

FDA는 1987년부터 사용한 공정 밸리데이션 가이드선을 수정하여 2008년 11월에 초안을 발간한 바 있으며, 2011년 1월 25일 최종판을 출간하였다. 초안과 비교하여 주목할 만한 변화는 다음과 같다.

- 위험기반 접근방식 강조
- 공정 개선
- 특성과 매개변수에 대한 용어는 이번 가이드선에서 언급되지 않음
- 바이러스성 불순물 제거를 위한 연구 내용 포함
- ‘Process Qualification’은 ‘Process Performance Qualification(공정성능 적격성 평가)’이라는 용어로 대체
- Stage 2(Process Qualification)에서 샘플링과 모니터링 강조
- ‘Drifts’라는 용어는 ‘비의도적인 공정 변이성’과 ‘원치 않는 공정 변이성’이라는 의미로 수정
- PPQ Batch의 동시적 출하와 관련된 설명 보충 : ‘동시적 출하’는 특별한 상황에서만 한다.
- 밸리데이션 문서화에 대한 유연성(정도와 종류) 요구
- 임상연구와 새로운 분석방법 사용에 관련된 설명 포함
- ASTM(American Society for Testing Materials, 미국시험재료협회) 규격 참고

※ Guidance for Industry

Process Validation: General Principles and Practices (p.602)

2 2011년 발간 예정 FDA 가이드런스 목록

2011년 1월 26일 FDA는 'New & Revised Draft Guidances CDER plans on publishing during the calendar year 2011'라는 가이드런스 목록을 발간하였다.

이 가이드런스는 다양한 카테고리로 구성되어 있으며, CGMP/Compliance와 관련 하여 많은 문서들이 실려 있다. 그 중 다음과 같은 내용은 산업계의 많은 주목을 받게 될 것이다.

- 위탁제조
- 효능이 강한 화합물의 관리
- 인체용 API의 수입
- Non-penicillin Beta-Lactam계 항생제 오염
- 의약품 성분 품질관리
- FDA 직원을 위한 Compliance Policy Guide(CPG) section 490.200 : 최종적으로 습열 멸균된 의약품의 매개변수출하

※ Guidance Agenda: New & Revised Draft Guidances CDER is Planning to Publish During Calendar Year 2011 (p.624)

3

FDA, “Non-Penicillin Beta Lactam Risk Assessment” 가이드라인 초안 발간

미국 연방법규 21 CFR §211.42(c)에는 페니실린의 제조, 공정, 포장에 별도의 시설에서 시행되어야 한다고 규정되어 있다. 여기서 “별도”란 반드시 분리된 건물을 의미하는 것은 아니며, 한 구역 이내의 격리로도 충분하다. 또한, §211.46(d)에서도 페니실린 제조를 위한 공기처리시스템은 다른 의약품으로부터 완전히 분리되어야 한다고 요구하고 있다.

2011년 3월에 발간된 가이드라인의 초안은 “Non-Penicillin Beta Lactam Risk Assessment : CGMP Framework(APIs 및 의약품의 제조에 적용되는 추천서)” Non-penicillin beta lactam계 항생제를 만들 때 이용되어지며 제조업자들이 별도 시설의 필요 여부를 결정하는데 도움을 줄 것이다.

Chapter 3은 FDA 권고사항이 포함되어 있으며 다른 Chapter에 비해 상대적으로 짧다.

FDA는 제조업자들이 별도의 시설에서 생산한 페니실린처럼 Non-Penicillin Beta Lactam계 제품도 정확하게 분리시켜 다룰 것이라 기대한다. FDA는 아래 사항의 교차 오염으로 인한 위험을 방지하기 위해 분리 및 제어에 대한 충분한 대책을 수립하도록 권고했다.

- Beta Lactam과 Non-Beta Lactam 제품
- Non-Penicillin Beta Lactam과 Non-Penicillin Beta Lactam 이외의 것들(교차 반응의 위험)

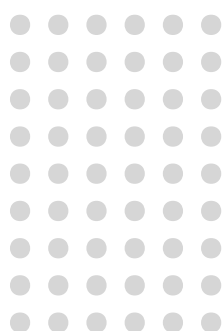
특정 종류의 Non-Penicillin Beta Lactam계(예를 들면, cephalosporin계) 항생제를 제조할 때 별도의 시설 및 공기처리시스템은 의무사항이 아니다.

FDA지시에 따라, 생산 운동(Production campaigning) 및 청소만으로도 충분할 것이다.

※ Guidance for Industry

Non-Penicillin Beta-Lactam Risk Assessment: A CGMP Framework DRAFT GUIDANCE (p.627)

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PART V

기타



1

ISPE, GAMP(Good Automated Manufacturing Practices)
5판 개정

2010년 초에 GAMP 우수관리 기준가이드(Good Practice Guide, GPG), A Risk-Based Approach to Operation of Gx P-Computerized Systems-A Companion Volume to GAMP 5가 발간되었다.

2008년, GAMP(Good Automated Manufacturing Practice)가이드 5판이 발간되어 컴퓨터 시스템 밸리데이션의 기준이 국제적으로 통용되기 시작하였다.

이번 새로운 GPG의 내용은 GAMP 5에 기초하고 있으며, 라이프사이클 동안의 특정 부분(실험 등) 또는 특별한 IT 시스템(MES* 등)에 초점을 맞추고 있다.

* MES(Manufacturing Execution System) : 현장에서 작업을 수행 시 필요한 제반 활동을 지원하기 위한 관리시스템으로, 현장 상태의 실시간 정보제공을 통하여 관리자와 작업자의 의사결정을 지원하는 기능을 수행

GPG는 GAMP의 부록을 준용하여 다음과 같이 구성되어 있다.

01. Introduction
02. Overview of the Operation Phase
03. What Organizations Should Do
04. Process Relationships
05. Handover
06. Establishing and Managing Support Services
07. Performance Monitoring
08. Incident Management
09. Corrective and Preventive Action
10. Operational Change and Configuration Management
11. Repair Activity
12. Periodic Review
13. Backup and Restore

14. Business Continuity Management
15. Security Management
16. System Administration
17. Data Migration
18. System Retirement, Decommissioning, and Disposal
19. Appendix1 - RACI Roles and Operational Processes
20. Appendix2 - Mapping of Operational Processes to ITIL® and COBIT®
21. Appendix3 - List of Control Records
22. Appendix4-References 23. Appendix5-Glossary

※ ISPE GAMP Good Practice Guide: A Risk-Based Approach to Operation of GxP Computerized Systems - A Companion Volume to GAMP 5

(출처 명시로 첨부 생략 http://www.techstreet.com/standards/ispe/ggpgogcs?product_id=1723506)

2 FDA, 의료기기 제조업체의 검사에 대한 가이드라인 초안 발간

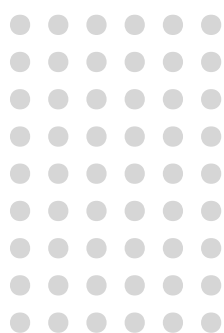
2010년 5월, FDA는 “Medical Device ISO 13485:2003 Voluntary Audit Report Submission Program; Availability”라는 제목의 가이드라인을 발간하였다. 이 가이드라인에 따르면 의료기기 제조업체는 자체 실사를 통한 결과에 대해 FDA로부터 평가를 받게 된다.

FDA는 이미 본 초안의 내용과 유사한 실사평가 프로그램을 의약품 제조업체를 대상으로 시범 운영하였으며, 그 결과를 바탕으로 실사주기 및 정도에 대한 설정이 가능하였다.

※ FOOD AND DRUG ADMINISTRATION COMPLIANCE PROGRAM GUIDANCE MANUAL- INSPECTION OF MEDICAL DEVICE MANUFACTURERS

(출처 명시로 첨부 생략 <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM212798.pdf>)

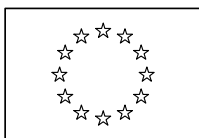
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첨부

가이드라인





EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods
Pharmaceuticals

Brussels, 14 February 2008

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines to
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Part I
Chapter 1 Quality Management

Document History	
Revision to include concept of Product Quality Review	25 October 2005
Date of revised version coming into operation and superseding previous version dated 25 October 2005	01 July 2008

Principle

The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice, Quality Control and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance system should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of the Manufacturing Authorisation and for the Qualified Person(s).

The basic concepts of Quality Assurance, Good Manufacturing Practice, Quality Control and Quality Risk Management are inter-related. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of medicinal products.

Quality Assurance

- 1.1 Quality Assurance is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide.

The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that:

- (i) medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice;
- (ii) production and control operations are clearly specified and Good Manufacturing Practice adopted;
- (iii) managerial responsibilities are clearly specified;
- (iv) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- (v) all necessary controls on intermediate products, and any other in-process controls and validations are carried out;
- (vi) the finished product is correctly processed and checked, according to the defined procedures;
- (vii) medicinal products are not sold or supplied before a Qualified Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products;
- (viii) satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

- (ix) there is a procedure for Self-Inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Quality Assurance system.

Good Manufacturing Practice for Medicinal Products (GMP)

1.2 Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation or product specification.

Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

- (i) all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;
- (ii) critical steps of manufacturing processes and significant changes to the process are validated;
- (iii) all necessary facilities for GMP are provided including:
 - appropriately qualified and trained personnel;
 - adequate premises and space;
 - suitable equipment and services;
 - correct materials, containers and labels;
 - approved procedures and instructions;
 - suitable storage and transport;
- (iv) instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
- (v) operators are trained to carry out procedures correctly;
- (vi) records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;
- (vii) records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- (viii) the distribution (wholesaling) of the products minimises any risk to their quality;
- (ix) a system is available to recall any batch of product, from sale or supply;
- (x) complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

Quality Control

- 1.3 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of Quality Control are that:

- (i) adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
- (ii) samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;
- (iii) test methods are validated;
- (iv) records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;
- (v) the finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorisation, are of the purity required, and are enclosed within their proper containers and correctly labelled;
- (vi) records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
- (vii) no batch of product is released for sale or supply prior to certification by a Qualified Person that it is in accordance with the requirements of the relevant authorisations;
- (viii) sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

Product Quality Review

1.4 Regular periodic or rolling quality reviews of all licensed medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

- (i) A review of starting materials including packaging materials used in the product, especially those from new sources.
- (ii) A review of critical in-process controls and finished product results.
- (iii) A review of all batches that failed to meet established specification(s) and their investigation.
- (iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.
- (v) A review of all changes carried out to the processes or analytical methods.
- (vi) A review of Marketing Authorisation variations submitted/granted/refused, including those for third country (export only) dossiers.
- (vii) A review of the results of the stability monitoring programme and any adverse trends.
- (viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time.
- (ix) A review of adequacy of any other previous product process or equipment corrective actions.
- (x) For new marketing authorisations and variations to marketing authorisations, a review of post-marketing commitments.
- (xi) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.
- (xii) A review of any contractual arrangements as defined in Chapter 7 to ensure that they are up to date.

The manufacturer and marketing authorisation holder should evaluate the results of this review, where different, and an assessment made of whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified.

Where the marketing authorisation holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The Qualified Person responsible for final batch certification together with the marketing authorisation holder should ensure that the quality review is performed in a timely manner and is accurate.

Quality Risk Management

1.5 Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

1.6 The quality risk management system should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient
- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk

Examples of the processes and applications of quality risk management can be found inter alia in Annex 20.



EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL
Public Health and Risk Assessment
Pharmaceuticals

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Chapter 5: Production

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: revision **for public consultation**

Deadline for public consultation: 28 February 2011

Reasons for changes: changes have been proposed to sections 25 and 26 on the qualification of suppliers of starting material in order to reflect the legal obligation of manufacturing authorisation holders to ensure that active substances are produced in accordance with GMP. Supply chain traceability for starting materials is also introduced in sections 26 and 27. A new section, 31, is proposed in order to clarify and harmonise expectations of manufacturers regarding the testing of starting materials. Further work on chapter 5 is ongoing, affecting section 19, as referred to in the Concept Papers published by EMA in February 2005. EMA also published progress reports on this work in February 2008 and December 2009.

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Principle

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorisations.

General

5.1 Production should be performed and supervised by competent people.

5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.

5.4 Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.

5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

5.6 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

5.7 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

5.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

5.9 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

5.10 At every stage of processing, products and materials should be protected from microbial and other contamination.

5.11 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitising materials.

5.12 At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

5.13 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean, ...).

5.14 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

5.15 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.

5.16 Access to production premises should be restricted to authorised personnel.

5.17 Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

Prevention of cross-contamination in production

5.18 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitising materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

5.19 Cross-contamination should be avoided by appropriate technical or organisational measures, for example:

- a) Production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;
- b) Providing appropriate air-locks and air extraction;

- c) Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
- d) Keeping protective clothing inside areas where products with special risk of cross contamination are processed;
- e) Using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
- f) Using “closed systems” of production;
- g) Testing for residues and use of cleaning status labels on equipment.

5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

Validation

5.21 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

5.22 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.23 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process, should be validated.

5.24 Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

Starting materials

5.25 Starting materials should only be purchased from manufacturers, importers or distributors of active substances approved by the manufacturers of medicinal products, named in the relevant specification and, where possible, directly from the manufacturer of the starting material. Purchase of starting materials should be controlled by written procedures. The supply chain of each starting materials should be known and be documented.

It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling, packaging and distribution requirements, as well as complaints and rejection procedures are discussed with the manufacturer and supplier, and that the outcome of these discussions are documented.

5.26 The selection, including qualification and approval of suppliers, and the purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers and the associated risks involved in that starting material's supply chain. Procedures for the assessment and purchase and acceptance of starting materials, including critical packaging materials should be documented as part of the quality management system. The approval of suppliers of starting materials should be

controlled by QC and production. Suppliers of active substances and, certain excipients considered to be high risk materials used as starting materials, should be periodically audited to confirm that they comply with current GMP requirements and that supply chain traceability¹ of the starting material is being maintained. The findings from each audit should be documented, and audit reports should be available for review by Inspectors.

5.27 For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels. Verification of the supply chain traceability should also be established and documented.

5.28 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

5.29 Starting materials in the storage area should be appropriately labelled (see Chapter 5, section 13). Labels should bear at least the following information:

- The designated name of the product and the internal code reference where applicable;
- a batch number given at receipt;
- Where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
- Where appropriate, an expiry date or a date beyond which retesting is necessary. When fully computerised storage systems are used, all the above information need not necessarily be in a legible form on the label.

5.30 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Chapter 6, section 13).

5.31 Manufacturers of the medicinal product are responsible for any testing of starting materials as described in the marketing authorisation dossier. Manufacturers of finished product can subcontract the testing of starting materials described in the marketing authorisation dossier to the approved starting material manufacturer but must, as a minimum, perform a confirmation of identity themselves.

The following requirements should be fulfilled when introducing subcontracting of partial or full testing:

- A formal agreement should be signed between the finished product manufacturer and the starting material manufacturer. Among the respective responsibilities described in the formal agreement, special attention should be paid to those related to the distribution conditions (transport, wholesaling, storage and delivery) in order to maintain the quality characteristics of the starting materials and to ensure that test results remain applicable to the delivered material.
- The finished product manufacturer should perform audits at appropriate intervals at the site(s) carrying out the testing (including sampling) of the starting materials in order to assure compliance with GMP and the specifications and testing methods described in the Marketing Authorisation.

¹ A record of where each active substance (including its critical starting materials) is manufactured, propagated, processed and handled prior to its use in the manufacture of a medicinal product. The record should include the names and addresses (including reference to the DUNS number) of each manufacturer, distributor, trader/broker and shipper involved in this part of the supply chain.

- The certificate of analysis provided by the starting material manufacturer should be signed by a designated person with appropriate qualifications and experience. This person should ensure that each batch has been manufactured and checked for compliance with the requirements of the formal agreement,
- Full analyses should be conducted on at least three different batches before reducing in-house testing. As a minimum, the finished product manufacturer should also perform a full analysis at appropriate intervals and compare the results with the supplier's Certificate of Analysis in order to check its reliability. Should this testing identify discrepancies then the acceptance of certificates of analysis from the supplier should be discontinued until investigations are completed.

Notes:

1. The same requirements apply to packaging materials as stated in GMP part I, 5.40.
2. Identity testing of starting materials should be performed according to the methods and the specifications of the relevant Marketing Authorisation dossier.

5.32 Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used.

5.33 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

5.34 Each dispensed material and its weight or volume should be independently checked and the check recorded.

5.35 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

Processing operations: intermediate and bulk products

5.36 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.

5.37 Intermediate and bulk products should be kept under appropriate conditions.

5.38 Critical processes should be validated (see "VALIDATION" in this Chapter).

5.39 Any necessary in-process controls and environmental controls should be carried out and recorded.

5.40 Any significant deviation from the expected yield should be recorded and investigated.

Packaging materials

5.41 The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

5.42 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorised access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorised personnel following an approved and documented procedure.

5.43 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

5.44 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

Packaging operations

5.45 When setting up a programme for the packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

5.46 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list.

5.47 The name and batch number of the product being handled should be displayed at each packaging station or line.

5.48 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

5.49 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

5.50 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

5.51 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

5.52 Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

5.53 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

5.54 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.55 On-line control of the product during packaging should include at least checking the following:

- a) general appearance of the packages;

- b) whether the packages are complete;
- c) whether the correct products and packaging materials are used;
- d) whether any over-printing is correct;
- e) correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

5.56 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.

5.57 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

5.58 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

Finished products

5.59 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

5.60 The evaluation of finished products and documentation necessary before release of product for sale is described in Chapter 6 (Quality Control).

5.61 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

Rejected, recovered and returned materials

5.62 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorised personnel.

5.63 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Records should be kept of the reprocessing.

5.64 The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorised beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

5.65 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.66 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken should be appropriately recorded.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 October 2010
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GMP/GDP IWG

Concept Paper on the Revision of Chapter 6 of the EU GMP Guide Quality Control

Agreed by GMP/GDP Inspectors Working Group	September 2010
Deadline for comments	28 February 2011

Comments should be provided using this [template](#). The completed comments form should be sent to ADM-GMDP@ema.europa.eu

Keywords	<i>GMP, Quality Control, Chapter 6</i>



1. Introduction

Chapter 6 of the EU GMP guide provides general guidance on the Quality Control Department and Good Quality Control Laboratory Practice including specific aspects for documentation, sampling and testing. General aspects for premises and equipment, documentation and the use of contract laboratories are linked to Chapters 3, 4 and 7, respectively, of the EU GMP guide.

2. Problem Statement

During inspections, GMP inspectors have noted that the root causes for suspected out-of-specification (OOS) results are sometimes attributed to a lack of test method validation in the context of transfer of analytical methods. Such situations also occur frequently at contract Quality Control laboratories.

3. Discussion

In the context of globalisation of manufacturing activities and the development of new concepts like Quality by Design, where technology transfer is expected to happen worldwide both within and between companies, within the same country as well as between countries, the need for guidance for transfer of analytical methods has been identified.

The revision process for Chapter 6 will also assess the need to take into consideration:

- the current guidance in Annexes 16, 19 and 20,
- the ICH Q8, Q9, Q10 documents,
- the draft document ICH Q11,
- the ongoing revision of Chapters 4, 7 and Annex 11,
- the development of new technologies such as Near Infrared Spectroscopy (NIR) in the context of raw material identification and Process Analytical Technology (PAT).

The need to provide specific guidance for endotoxin and microbiological testing will also be considered.

4. Recommendation

It is therefore recommended that a specific section of Chapter 6 should be developed to provide guidance to industry and Inspectors for the transfer of analytical methods from one laboratory to another.

The content of Chapter 6 should also be reviewed to include guidance on technical transfer in conjunction with the new concepts and guidelines mentioned above.

5. Proposed Timetable

- Adoption of the Concept Paper by the GMP/GDP IWG at the September meeting in 2010.
- Preparation of a first draft by the drafting group by the September 2011 meeting of GMP/GDP IWG.
- Discussion on the draft at the September 2011 meeting during the joint meeting with the QWP. BWP will also be consulted for comments.

- Adoption of the final draft at the February 2012 meeting.
- It is anticipated that the start of consultation on a new guideline could be achieved after the February 2011 meeting.
- Public consultation for a minimum of three months (approximately June 2012).
- Adoption of the final document by GMP GDP IWG during the last meeting in 2012 for adoption and publication by the European Commission.

6. Resource Requirements for Preparation

A drafting group of Inspectors has already been identified with United Kingdom (H), Ireland, EDQM and France (H) as rapporteur. The drafting group will liaise and exchange experiences with OMCLs. The drafting group will meet via teleconference as well as at dedicated drafting group meetings of which three or four may be required.

7. Impact Assessment (Anticipated)

The clear requirements for transfer of analytical methods would be the main factor which would impact additional burden on companies because at the moment, some of them have not implemented such a process.

Others changes would include clarification of guidance but would not have resource implications. These changes would facilitate a harmonised regulatory policy.

The impact on Annex 8 will also be considered in the context of identification of raw materials.

8. Interested Parties

The drafting group will liaise and exchange experiences from PIC/S and MRA partners.

The draft guideline will be made publicly available to interested parties for a minimum 3 month consultation period before finalisation.

9. References to Literature, Guidelines etc.

1. Guideline of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q2 (R1): Validation of Analytical procedures: Text and Methodology.
2. The European Pharmacopoeia.
3. Official Medicines Control Laboratories Network or the Council of Europe, Quality Assurance Documents: PA/PH/OMCL (05) 47 DEF – Validation of Analytical Procedures.
4. WHO guideline on Transfer of technology. Draft Document QAS/08.259 rev 1, September 2009.
5. WHO Good practices for pharmaceutical quality control laboratories. Draft Document QAS/09.296 May 2009.
6. The U.S. Pharmacopoeia., 31st edition. General chapters: < 1225> Validation of compendial procedures, 2009.

7. ICH Harmonized tripartite Guideline. Pharmaceutical development. Q8
8. ICH Harmonized tripartite Guideline. Quality Risk Management. Q9
9. ICH Harmonized tripartite Guideline. Pharmaceutical Quality System. Q10
10. ICH Harmonized tripartite drafted Guideline Development and Manufacture of Drugs Substances Q11,
11. EU GMP Guide, Annexes 8,16 and 19.
12. Draft or adopted version of chapter 4 and Annex 11.
13. Draft or adopted version of the Note for Guidance for Near Infrared Spectroscopy.



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Volume 4
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Chapter 7: Outsourced Activities

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: revision for public consultation

Deadline for public consultation: 28 February 2011

Reasons for changes: in view of the ICH Q10 guideline on the Pharmaceutical Quality System, Chapter 7 of the GMP Guide has been revised in order to provide updated guidance on outsourced GMP regulated activities beyond the current scope of contract manufacture and analysis operations. The title of the Chapter has been changed to reflect this.

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The Contract

Principle

Outsourced activities must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The Quality System of the Contract Giver must clearly state the way that the Qualified Person certifying each batch of product for release exercises his full responsibility.

Note: This Chapter deals with the responsibilities of manufacturers towards the Competent Authorities of the Member States with respect to the granting of marketing and manufacturing authorizations. It is not intended in any way to affect the respective liability of contract acceptors and contract givers to consumers; this is governed by other provisions of Union and national law.

General

- 7.1 There should be a written contract covering the outsourced activities, the products or operations to which they are related, and any technical arrangements made in connection with it.
- 7.2 All arrangements for the outsourced activities including any proposed changes in technical or other arrangements should be in accordance with regulations in force, and the Marketing Authorisation for the product concerned.

The Contract Giver

- 7.3 The pharmaceutical quality system of the Contract Giver, including the management responsibilities, extends to the control and review of any outsourced activities. The Contract Giver is ultimately responsible to ensure processes are in place to assure the control of outsourced activities. These processes should incorporate quality risk management.
- 7.4 Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor and, if applicable, his mutually agreed subcontractors to carry out successfully the outsourced activities required using a defined supply chain (e.g. audits, material evaluations, qualification) and for ensuring by means of the contract that the principles and guidelines of GMP as interpreted in this Guide are followed.

- 7.5 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.
- 7.6 The Contract Giver should monitor and review of the performance of the contract acceptor and the identification and implementation of any needed improvement.
- 7.7 The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. He should also ensure that all processed products and materials delivered to him by the Contract Acceptor comply with their specifications or that the products have been released by a Qualified Person.

The Contract Acceptor

- 7.8 The Contract Acceptor must be able to carry out satisfactorily the work ordered by the Contract Giver such as having adequate premises, equipment, knowledge, experience, and competent personnel.
- 7.9 The Contract Acceptor should ensure that all products, materials and knowledge delivered to him are suitable for their intended purpose.
- 7.10 The Contract Acceptor should not subcontract to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that information and knowledge, including those from assessments of the suitability of the third party, are made available in the same way as between the original Contract Giver and Contract Acceptor.
- 7.11 The Contract Acceptor should not make unauthorized changes, which may adversely affect the quality of the outsourced activities for the contract giver.

The Contract

- 7.12 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice.

- 7.13 The contract should describe clearly who is responsible for each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis). In the case of contract analysis, the contract should state whether or not the Contract Acceptor should take samples at the premises of the manufacturer.
- 7.14 All records related to the outsourced activities, e.g. manufacturing, analytical and distribution records, and reference samples, should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the Contract Giver.
- 7.15 The contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or his mutually agreed subcontractors
- 7.16 In the case of contract analysis, the Contract Acceptor should understand that he is subject to inspection by the competent Authorities

The New GMP Annex 11 and Chapter 4 is Europe's Answer to Part 11

As mentioned in the last GMP newsletter, this month saw the publication of the new revision of European Union (EU) GMP Annex 11 on Computerised Systems and Chapter 4 on Documentation. The impact of these new revisions is extensive as combined they are the equivalent to the FDA's Part 11 regulation for electronic records and signatures. This will be a high level look at both new regulations but for full details please read the full versions of each.

Annex 11 Changes

1. Increased Scope of Annex 11

The first section to discuss is the Principle that covers the scope and application of the new regulation. The key elements of the Principle are:

- *Annex 11 applies to all forms computerised systems used as part of a GMP regulated activities.*
This is a wide scope statement and includes all computerised systems including the in-house developed spreadsheets and databases.
- *The application should be validated; IT infrastructure should be qualified.*
This is the major item: the ten words that mean so much validate applications and qualify infrastructure. For the first time in any regulation there is a specific requirement for IT infrastructure qualification.
- *When a computerised system replaces a manual process there should be no resultant decrease in product quality, process control or quality assurance.*
In a carry over from the current version of Annex 11 there is the additional requirement of process control. In essence, it mandates the minimum the quality of a computerised system should be as good as the manual system it replaces but in reality, the computerised system should be much better as the human factor is usually taken out of the process.

2. Risk Management throughout the System Life Cycle

Annex 11 has always had risk management but it has been buried in the detail: under validation of systems the amount of validation work required was dependent on the nature of the software. Now we have a new section requiring risk management to be applied throughout the life cycle of a computerised system dependent on patient safety, data integrity and product quality. The work done should be based on a "*justified and documented risk assessment*", wording that has been borrowed from the FDA.

3. New Roles and Responsibilities Defined

In section 2 on Personnel there still remains the requirement for close cooperation between all involved with the system including IT from the earlier version. However we have new two new roles mentioned and defined in the glossary:

- **Process owner:** the person responsible for the business process. The individual in this case would typically be a senior manager.
- **System owner:** the person responsible for the availability and maintenance of a computerised system and the security of the data residing on that system (typically a senior spectroscopist or laboratory manager).

4. Suppliers and Service Providers

This area is a major expansion of Annex 11 that moves from a single sentence into four clauses which catches up with technology and organisational changes that have occurred since the original version of the regulation was issued. When third parties are used to carry out any work on a computerised system there needs to be a formal agreement (contract or service level agreement) clause 3.1 notes that there should be "*clear statements of the responsibilities of the third party*". Then there is a short sentence stating "*IT departments should be considered analogous*" which means that even if an organisation's own IT department is used to support a validated computerised system they need to

have a service level agreement with the regulated laboratory. There may also be the need for an audit of a supplier or service provider and the decision for this should be based on a risk assessment.

When an audit is performed, the new regulation requires that the “quality system and audit information” is available to inspectors on request. This is a major departure from regulations and current practices, typically an audit report is seen as an internal quality assurance document by many companies and only the evidence that an audit took place will be a certificate given to an inspector. However, there is major regulatory concern with the supply chain and software and services are included in this that regulators in Europe are taking a hard line and want to see the audit reports to satisfy themselves that the service of product for critical operations has the quality built into it.

5. Validation

The validation section has been expanded from one to eight clauses. The key changes are that a life cycle should be used to validate a system and that manufacturers should be able to justify their approaches based on risk assessment. The Annex 11 update does not mandate any validation approach but whichever one is selected for a specific system it needs to be justified and documented to withstand regulatory scrutiny. Some administrative requirements for validation are an inventory for computerised systems although this would have been useful to link with the validation master plan in Annex 15 and for critical systems there needs to be a current system description. In effect the requirement for an inventory formalises what is usually required for an inspection and the system description is limited now to critical rather than all systems as required by the old version.

For each computerised system validation there needs to be a user requirements specification to describe the required functions of the system based on risk assessment and GMP impact. Furthermore there is now the need for requirements traceability throughout the life cycle, for the first time in a regulation a traceability matrix is required. The tests method and test scenarios need to be documented and applies and testing should include the overall process with consideration of data limits, parameter limits and error handling. The latter is particularly important to know before a system becomes operational than when discussing this with an inspector. Annex 11 also allows the use of automated test tools and test environments providing that they have documented assessments for their adequacy for the task. Before you all rush off and spend money on automated test tools bear in mind an assessment by Frewster and Graham that you need to be able to operate a test tool between 8 and 11 times before you break even on your investment. There will be very few laboratory systems that will require automated testing.

6. Controls for Ensuring Data Integrity

Sections 5, 6, 8, 9 and 12 cover the main elements of data integrity (data, accuracy, audit trails and security) in the new Annex 11. In summary, these sections are looking for checks for correct and secure entry (both manually entered and automatically captured data) and the subsequent data processing to minimise the risks of a wrong decision based on wrong results. The identity of authorised individuals carrying out work needs to be added to records including data and time stamps of entries, changes and deletions and records maintained of who can access a system along with their access privileges. Further controls are required to secure data by both physical and electronic means against damage and that stored data need to be checked for accessibility, readability and accuracy and this applies to both paper and electronic records.

Print outs both of electronically stored data and any records used to support batch release need to be available. There is also a specific requirement for any print out supporting batch release to indicate if any data has been changed since the original entry, presumably so the Qualified Person can check what has happened. However, most vendors will point to the audit trail search function as the means to fulfil this requirement. This is inadequate. What is required is that when the result is printed out, there is an annotation or equivalent to indicate if the result has been changed or not. Chromatography data systems have this for baseline fits: unchanged baseline fits are in capital letters and manually changed ones are in lower case.

Audit trails are not mandatory on all systems but should be based on risk assessment. Personally, if you are going to work electronically, then an audit trail is essential to ensuring data integrity. Mirroring some of the recent FDA warning letters, the new Annex 11 requires audit trails to be “*available and*

convertible to a generally intelligible form and be regularly reviewed". The problem is that many audit trails are simply depositories of unintelligible rubbish and how will vendors show that the audit trail has been reviewed?

In addition, there are requirements for data migration (section 4.8) and archiving (section 17) to ensure that electronic records acquired in one version of software can be read in a new version as well as allowing data to be archived. However in the latter case the data should be assessed for "*accessibility, readability and integrity*" especially after changes made to the software or the IT infrastructure.

7. Electronic Signatures

The new version also sees the formalisation of electronic signatures in EU GMP. Many laboratories have implemented electronic signatures based on 21 CFR 11 but the European regulation does not appear as stringent as the US regulation. The requirements for electronic signatures to have the same impact as hand written signatures within the boundaries of the company, be permanently linked to the respective record and include the time and date that a signature was applied. There is not the stated bureaucracy and formality of 21 CFR 11 to send letters the FDA, have no repudiation of an electronic signature requirements or the three different types of signature. However many of the same requirements are implicit as the European legislation simply states that electronic signatures have the same impact as handwritten signatures and hence all of the non-repudiation requirements apply immediately.

8. IT Support of Validated Systems

The current Annex 11 requirements of backup, security, incident management, business continuity and been carried over to the new version and expanded. Backups (section 7.2) need to be performed regularly but the new version has expanded the requirement to include checks for the integrity and accuracy of backup data and the ability to restore data check during the validation and also periodically thereafter. This is intended to ensure that backup media can still be read throughout the record retention period. Security also includes the network as well as individual applications and the extent of controls depends on the criticality of the application but also if you are accessing it from inside or outside the organisation.

Incident management has changed from a simple statement of "*any failures and remedial action should be recorded*" to "*all incidents, not only system failures and data errors, should be reported and assessed*". So the scope has been widened greatly. However, the new version goes further "*The root cause of a critical incident should be identified and should form the basis of corrective and preventative actions*". So implied within this process should be a means to assess and classify errors and then for the critical ones only undertake a root cause analysis and then formulate both corrective and preventative action plans. It is this portion of the new regulation that will impact many incident management processes.

Again, business continuity was covered in clauses 15 and 16 in the old regulation which have been consolidated in to the single clause 16 in the new version. What is required is to have plans available to ensure continuity of support for critical processes as well as knowing the time required to bring alternatives into operation based on risk assessments. However the new regulation specifically requires that these arrangements need to be documented and tested adequately before use.

9. Maintaining Validation

A brand new requirement comes in the shape of a formal periodic evaluation, otherwise known as a periodic review, to ensure that they remain in a validated state. This formalises what a number of companies already do and should cover the last full validation and changes made since then versus current functionality, deviations and incidents, upgrades and security which will be documented in a report.

Change control has been an original part of Annex 11 and it remains in the new version with an extension to include configuration management. Controlling changes is the most important part of maintaining the validation status of a computerised system and a procedure needs to be defined and

under the validation section earlier should involve risk assessment (clause 1) and be documented (clause 4.2). The problem with clause 10 is that it mentions configuration management but this is not defined in the glossary nor mentioned in the text. Another fine (regulatory) mess! What is required? We do not know if configuration management is meant in the context of management of modules of software code, components (configuration items) of the computerised system or both.

Chapter 4 – Documentation

The new version of Chapter 4 ("Documentation") of the EU Guideline to GMP was also published at the same time as Annex 11 and will also become effective on 30 June 2011. The clue to its impact comes in the reason for change of the sections on generation and control of documentation and retention of documents sections *"in light of the increasing use of electronic documents within the GMP environment"*. Furthermore in the principle section it states that *"Documentation may exist in a variety of forms, including paper based, electronic or photographic media"*. This is close to the definition of electronic record in 21 CFR 11 except in Europe for electronic record read documentation.

The European regulators have defined the expected GMP document types in far more detail than their US counterparts, thus making it far easier to understand and implement the new regulation in practice.

Of particular interest are records, which are defined as:

- *Provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution.*
This means that if you follow a procedure or an analytical method there needs to be evidence that the procedure or instruction was followed. Traditionally this is by printing data or results but, as you remember the reason for the update of Chapter 4 was the increased use of electronic documentation, so the next section states:
- *Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data.*
This is one of the major impacts of Chapter 4, the definition of electronic raw data. Therefore electronic records which are used to make quality decisions should be defined as raw data; you realize that when a regulation says should it really means must.
- Furthermore the records used for batch release must be made available to the Qualified Person and also if there have been any changes made to the record, then these need to be flagged for review.

Generation and Control of Documentation

Under this section, in clause 4.1 it states that all types of documents should be defined and adhered to and they apply to all media types. This clause then discusses hybrid and homogeneous documents in further detail.

Many documents (instructions and/or records) may exist in hybrid forms, i.e. some elements as electronic and others as paper based. Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogenous systems. Appropriate controls for electronic documents such as templates, forms, and master documents should be implemented. Appropriate controls should be in place to ensure the integrity of the record throughout the retention period.

So let us dissect this section in a little more detail. Regardless of the fact that a document (including a record i.e. analytical result) is homogeneous (either paper or electronic) or hybrid (electronic with a paper printout) the control mechanisms need to be defined, documented and implemented. One key requirement that both the FDA and Europeans agree on is record or data integrity: what controls are needed to ensure the record is a true and accurate one? The typical response from the regulator is "appropriate" – therefore more critical records need more stringent controls. This has been discussed in some detail in the GAMP Good Practice Guide on Part 11 Electronic Records and Signatures compliance and is outside of the scope of this column.

Retention of Documents

Batch records, including those in electronic format, now need to be defined for each manufacturing activity and also where each record is located. Once the storage location is defined there need to be security controls implemented to ensure record integrity throughout the retention period. Where records are stored electronically, the integrity and security controls need to be validated.

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Pharmaceutical Quality System (ICH Q10)

The ICH Q10 document on Pharmaceutical Quality System was adopted at Step 4 at the ICH Steering Committee meeting in June 2008.

By virtue of Article 6 of Directive 2003/94/EC and Directive 91/412/EEC manufacturing authorisation holders are already obliged to establish and implement an effective pharmaceutical quality assurance system in order to comply with Good Manufacturing Practice (GMP) and guidance is provided in Chapter 1 of the GMP Guide.

ICH Q10 provides an example of a pharmaceutical quality system designed for the entire product lifecycle and therefore goes beyond current GMP requirements, which with the exception of the manufacture of investigational medicinal products for human use, do not apply to the development part of the lifecycle. At the time of the EU implementation of ICH Q10 it was also recognised that Chapters 1, 2 and 7 of the GMP Guide should be updated to align with the terminology and concepts utilised in ICH Q10.

The content of ICH Q10 that is additional to the scope of GMP is optional. Its use should facilitate innovation, continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.



Pharmaceutical Quality System (ICH Q10)

ICH harmonised tripartite guideline

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1. Pharmaceutical quality system

1.1. Introduction

This document establishes a new ICH tripartite guideline describing a model for an effective quality management system for the pharmaceutical industry, referred to as the Pharmaceutical Quality System. Throughout this guideline, the term “pharmaceutical quality system” refers to the ICH Q10 model.

ICH Q10 describes one comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organisation (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q8 “Pharmaceutical Development” and ICH Q9 “Quality Risk Management”. ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements. ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional.

ICH Q10 demonstrates industry and regulatory authorities’ support of an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health. Implementation of ICH Q10 throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

1.2. Scope

This guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances (i.e., API) and drug products, including biotechnology and biological products, throughout the product lifecycle.

The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the differences among, and the different goals of each stage (see Section 3).

For the purposes of this guideline, the product lifecycle includes the following technical activities for new and existing products:

- Pharmaceutical Development
 - Drug substance development;
 - Formulation development (including container/closure system);
 - Manufacture of investigational products;
 - Delivery system development (where relevant);
 - Manufacturing process development and scale-up;
 - Analytical method development.

- Technology transfer
 - New product transfers during development through manufacturing;
 - Transfers within or between manufacturing and testing sites for marketed products.
- Commercial manufacturing
 - Acquisition and control of materials;
 - Provision of facilities, utilities, and equipment;
 - Production (including packaging and labelling);
 - Quality control and assurance;
 - Release;
 - Storage;
 - Distribution (excluding wholesaler activities).
- Product discontinuation
 - Retention of documentation;
 - Sample retention;
 - Continued product assessment and reporting.

1.3. Relationship of ICH Q10 to regional GMP requirements, ISO standards and ICH Q7

Regional GMP requirements, the ICH Q7 Guideline, “Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients”, and ISO quality management system guidelines form the foundation for ICH Q10. To meet the objectives described below, ICH Q10 augments GMP by describing specific quality system elements and management responsibilities. ICH Q10 provides a harmonised model for a pharmaceutical quality system throughout the lifecycle of a product and is intended to be used together with regional GMP requirements.

The regional GMPs do not explicitly address all stages of the product lifecycle (e.g., Development). The quality system elements and management responsibilities described in this guideline are intended to encourage the use of science and risk based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle.

1.4. Relationship of ICH Q10 to regulatory approaches

Regulatory approaches for a specific product or manufacturing facility should be commensurate with the level of product and process understanding, the results of quality risk management, and the effectiveness of the pharmaceutical quality system. When implemented, the effectiveness of the pharmaceutical quality system can normally be evaluated during a regulatory inspection at the manufacturing site. Potential opportunities to enhance science and risk based regulatory approaches are identified in Annex 1. Regulatory processes will be determined by region.

1.5. ICH Q10 objectives

Implementation of the Q10 model should result in achievement of three main objectives which complement or enhance regional GMP requirements.

1.5.1. Achieve product realisation

To establish, implement and maintain a system that allows the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers.

1.5.2. Establish and maintain a state of control

To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes. Quality risk management can be useful in identifying the monitoring and control systems.

1.5.3. Facilitate continual improvement

To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfill quality needs consistently. Quality risk management can be useful for identifying and prioritising areas for continual improvement.

1.6. Enablers: knowledge management and quality risk management

Use of knowledge management and quality risk management will enable a company to implement ICH Q10 effectively and successfully. These enablers will facilitate achievement of the objectives described in Section 1.5 above by providing the means for science and risk based decisions related to product quality.

1.6.1. Knowledge management

Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding. Knowledge management is a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components. Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and change management activities.

1.6.2. Quality risk management

Quality risk management is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality. It facilitates continual improvement of process performance and product quality throughout the product lifecycle. ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.

1.7. Design and content considerations

- (a) The design, organisation and documentation of the pharmaceutical quality system should be well structured and clear to facilitate common understanding and consistent application.
- (b) The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the different goals and knowledge available for each stage.
- (c) The size and complexity of the company's activities should be taken into consideration when developing a new pharmaceutical quality system or modifying an existing one. The design of the pharmaceutical quality system should incorporate appropriate risk management principles. While some aspects of the pharmaceutical quality system can be company-wide and others site-specific, the effectiveness of the pharmaceutical quality system is normally demonstrated at the site level.
- (d) The pharmaceutical quality system should include appropriate processes, resources and responsibilities to provide assurance of the quality of outsourced activities and purchased materials as described in Section 2.7.
- (e) Management responsibilities, as described in Section 2, should be identified within the pharmaceutical quality system.
- (f) The pharmaceutical quality system should include the following elements, as described in Section 3: process performance and product quality monitoring, corrective and preventive action, change management and management review.
- (g) Performance indicators, as described in Section 4, should be identified and used to monitor the effectiveness of processes within the pharmaceutical quality system.

1.8. Quality manual

A Quality Manual or equivalent documentation approach should be established and should contain the description of the pharmaceutical quality system. The description should include:

- (a) The quality policy (see Section 2);
- (b) The scope of the pharmaceutical quality system;
- (c) Identification of the pharmaceutical quality system processes, as well as their sequences, linkages and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting pharmaceutical quality system processes in a visual manner;
- (d) Management responsibilities within the pharmaceutical quality system (see Section 2).

2. Management responsibility

Leadership is essential to establish and maintain a company-wide commitment to quality and for the performance of the pharmaceutical quality system.

2.1. Management commitment

- (a) Senior management has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the quality objectives, and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the company.

(b) Management should:

- (1) Participate in the design, implementation, monitoring and maintenance of an effective pharmaceutical quality system;
- (2) Demonstrate strong and visible support for the pharmaceutical quality system and ensure its implementation throughout their organisation;
- (3) Ensure a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management;
- (4) Define individual and collective roles, responsibilities, authorities and inter-relationships of all organisational units related to the pharmaceutical quality system. Ensure these interactions are communicated and understood at all levels of the organisation. An independent quality unit/structure with authority to fulfill certain pharmaceutical quality system responsibilities is required by regional regulations;
- (5) Conduct management reviews of process performance and product quality and of the pharmaceutical quality system;
- (6) Advocate continual improvement;
- (7) Commit appropriate resources.

2.2. Quality policy

- (a) Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality.
- (b) The quality policy should include an expectation to comply with applicable regulatory requirements and should facilitate continual improvement of the pharmaceutical quality system.
- (c) The quality policy should be communicated to and understood by personnel at all levels in the company.
- (d) The quality policy should be reviewed periodically for continuing effectiveness.

2.3. Quality planning

- (a) Senior management should ensure the quality objectives needed to implement the quality policy are defined and communicated.
- (b) Quality objectives should be supported by all relevant levels of the company.
- (c) Quality objectives should align with the company's strategies and be consistent with the quality policy.
- (d) Management should provide the appropriate resources and training to achieve the quality objectives.
- (e) Performance indicators that measure progress against quality objectives should be established, monitored, communicated regularly and acted upon as appropriate as described in Section 4.1 of this document.

2.4. Resource management

- (a) Management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness.
- (b) Management should ensure that resources are appropriately applied to a specific product, process or site.

2.5. Internal communication

- (a) Management should ensure appropriate communication processes are established and implemented within the organisation.
- (b) Communications processes should ensure the flow of appropriate information between all levels of the company.
- (c) Communication processes should ensure the appropriate and timely escalation of certain product quality and pharmaceutical quality system issues.

2.6. Management review

- (a) Senior management should be responsible for pharmaceutical quality system governance through management review to ensure its continuing suitability and effectiveness.
- (b) Management should assess the conclusions of periodic reviews of process performance and product quality and of the pharmaceutical quality system, as described in Sections 3 and 4.

2.7. Management of outsourced activities and purchased materials

The pharmaceutical quality system, including the management responsibilities described in this section, extends to the control and review of any outsourced activities and quality of purchased materials. The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. These processes should incorporate quality risk management and include:

- (a) Assessing prior to outsourcing operations or selecting material suppliers, the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g., audits, material evaluations, qualification);
- (b) Defining the responsibilities and communication processes for quality-related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor;
- (c) Monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and the identification and implementation of any needed improvements;
- (d) Monitoring incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.

2.8. Management of change in product ownership

When product ownership changes, (e.g., through acquisitions) management should consider the complexity of this and ensure:

- (a) The ongoing responsibilities are defined for each company involved;
- (b) The necessary information is transferred.

3. Continual improvement of process performance and product quality

This section describes the lifecycle stage goals and the four specific pharmaceutical quality system elements that augment regional requirements to achieve the ICH Q10 objectives, as defined in Section 1.5. It does not restate all regional GMP requirements.

3.1. Lifecycle stage goals

The goals of each product lifecycle stage are described below.

3.1.1. Pharmaceutical development

The goal of pharmaceutical development activities is to design a product and its manufacturing process to consistently deliver the intended performance and meet the needs of patients and healthcare professionals, and regulatory authorities and internal customers' requirements. Approaches to pharmaceutical development are described in ICH Q8. The results of exploratory and clinical development studies, while outside the scope of this guidance, are inputs to pharmaceutical development.

3.1.2. Technology transfer

The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement.

3.1.3. Commercial manufacturing

The goals of manufacturing activities include achieving product realisation, establishing and maintaining a state of control and facilitating continual improvement. The pharmaceutical quality system should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded.

3.1.4. Product discontinuation

The goal of product discontinuation activities is to manage the terminal stage of the product lifecycle effectively. For product discontinuation, a pre-defined approach should be used to manage activities such as retention of documentation and samples and continued product assessment (e.g., complaint handling and stability) and reporting in accordance with regulatory requirements.

3.2. Pharmaceutical quality system elements

The elements described below might be, required in part under regional GMP regulations. However, the Q10 model's intent is to enhance these elements in order to promote the lifecycle approach to product quality. These four elements are:

- Process performance and product quality monitoring system;
- Corrective action and preventive action (CAPA) system;
- Change management system;
- Management review of process performance and product quality.

These elements should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the differences among, and the different goals of, each stage. Throughout the product lifecycle, companies are encouraged to evaluate opportunities for innovative approaches to improve product quality.

Each element is followed by a table of example applications of the element to the stages of the pharmaceutical lifecycle.

3.2.1. Process performance and product quality monitoring system

Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained. An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement. The process performance and product quality monitoring system should:

- (a) Use quality risk management to establish the control strategy. This can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. The control strategy should facilitate timely feedback/feed-forward and appropriate corrective action and preventive action;
- (b) Provide the tools for measurement and analysis of parameters and attributes identified in the control strategy (e.g., data management and statistical tools);
- (c) Analyse parameters and attributes identified in the control strategy to verify continued operation within a state of control;
- (d) Identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation;
- (e) Include feedback on product quality from both internal and external sources, e.g., complaints, product rejections, non-conformances, recalls, deviations, audits and regulatory inspections and findings;
- (f) Provide knowledge to enhance process understanding, enrich the design space (where established), and enable innovative approaches to process validation.

Table I: Application of process performance and product quality monitoring system throughout the product lifecycle

Pharmaceutical development	Technology transfer	Commercial manufacturing	Product discontinuation
Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.

3.2.2. Corrective Action and Preventive Action (CAPA) system

The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring. A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9. CAPA methodology should result in product and process improvements and enhanced product and process understanding.

Table II: Application of corrective action and preventive action system throughout the product lifecycle

Pharmaceutical development	Technology transfer	Commercial manufacturing	Product discontinuation
Product or process variability is explored. CAPA methodology is useful where corrective actions and preventive actions are incorporated into the iterative design and development process.	CAPA can be used as an effective system for feedback, feed-forward and continual improvement.	CAPA should be used and the effectiveness of the actions should be evaluated.	CAPA should continue after the product is discontinued. The impact on product remaining on the market should be considered as well as other products which might be impacted.

3.2.3. Change management system

Innovation, continual improvement, the outputs of process performance and product quality monitoring and CAPA drive change. In order to evaluate, approve and implement these changes properly, a company should have an effective change management system. There is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission, where changes to the regulatory filing might be required under regional requirements.

The change management system ensures continual improvement is undertaken in a timely and effective manner. It should provide a high degree of assurance there are no unintended consequences of the change.

The change management system should include the following, as appropriate for the stage of the lifecycle:

- (a) Quality risk management should be utilised to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk;
- (b) Proposed changes should be evaluated relative to the marketing authorisation, including design space, where established, and/or current product and process understanding. There should be an assessment to determine whether a change to the regulatory filing is required under regional requirements. As stated in ICH Q8, working within the design space is not considered a change (from a regulatory filing perspective). However, from a pharmaceutical quality system standpoint, all changes should be evaluated by a company's change management system;
- (c) Proposed changes should be evaluated by expert teams contributing the appropriate expertise and knowledge from relevant areas (e.g., Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs and Medical), to ensure the change is technically justified. Prospective evaluation criteria for a proposed change should be set;
- (d) After implementation, an evaluation of the change should be undertaken to confirm the change objectives were achieved and that there was no deleterious impact on product quality.

Table III: Application of change management system throughout the product lifecycle

Pharmaceutical development	Technology transfer	Commercial manufacturing	Product discontinuation
Change is an inherent part of the development process and should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development.	The change management system should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science and risk based assessments.	Any changes after product discontinuation should go through an appropriate change management system.

3.2.4. Management review of process performance and product quality

Management review should provide assurance that process performance and product quality are managed over the lifecycle. Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management and should include a timely and effective communication and escalation process to raise appropriate quality issues to senior levels of management for review.

- (a) The management review system should include:
 - (1) The results of regulatory inspections and findings, audits and other assessments, and commitments made to regulatory authorities;
 - (2) Periodic quality reviews, that can include:
 - (i) Measures of customer satisfaction such as product quality complaints and recalls;
 - (ii) Conclusions of process performance and product quality monitoring;
 - (iii) The effectiveness of process and product changes including those arising from corrective action and preventive actions.
 - (3) Any follow-up actions from previous management reviews.
- (b) The management review system should identify appropriate actions, such as:
 - (1) Improvements to manufacturing processes and products;
 - (2) Provision, training and/or realignment of resources;
 - (3) Capture and dissemination of knowledge.

Table IV: Application of management review of process performance and product quality throughout the product lifecycle

Pharmaceutical development	Technology transfer	Commercial manufacturing	Product discontinuation
Aspects of management review can be performed to ensure adequacy of the product and process design.	Aspects of management review should be performed to ensure the developed product and process can be manufactured at commercial scale.	Management review should be a structured system, as described above, and should support continual improvement.	Management review should include such items as product stability and product quality complaints.

4. Continual improvement of the pharmaceutical quality system

This section describes activities that should be conducted to manage and continually improve the pharmaceutical quality system.

4.1. Management review of the pharmaceutical quality system

Management should have a formal process for reviewing the pharmaceutical quality system on a periodic basis. The review should include:

- (a) Measurement of achievement of pharmaceutical quality system objectives;
- (b) Assessment of performance indicators that can be used to monitor the effectiveness of processes within the pharmaceutical quality system, such as:
 - (1) Complaint, deviation, CAPA and change management processes;
 - (2) Feedback on outsourced activities;
 - (3) Self-assessment processes including risk assessments, trending, and audits;
 - (4) External assessments such as regulatory inspections and findings and customer audits.

4.2. Monitoring of internal and external factors impacting the pharmaceutical quality system

Factors monitored by management can include:

- (a) Emerging regulations, guidance and quality issues that can impact the Pharmaceutical Quality System;
- (b) Innovations that might enhance the pharmaceutical quality system;
- (c) Changes in business environment and objectives;
- (d) Changes in product ownership.

4.3. Outcomes of management review and monitoring

The outcome of management review of the pharmaceutical quality system and monitoring of internal and external factors can include:

- (a) Improvements to the pharmaceutical quality system and related processes;
- (b) Allocation or reallocation of resources and/or personnel training;
- (c) Revisions to quality policy and quality objectives;
- (d) Documentation and timely and effective communication of the results of the management review and actions, including escalation of appropriate issues to senior management.

5. Glossary

ICH and ISO definitions are used in ICH Q10 where they exist. For the purpose of ICH Q10, where the words "requirement", "requirements" or "necessary" appear in an ISO definition, they do not necessarily reflect a regulatory requirement. The source of the definition is identified in parentheses after the definition. Where no appropriate ICH or ISO definition was available, an ICH Q10 definition was developed.

Capability of a process:

Ability of a process to realise a product that will fulfill the requirements of that product. The concept of process capability can also be defined in statistical terms. (ISO 9000:2005)

Change management:

A systematic approach to proposing, evaluating, approving, implementing and reviewing changes. (ICH Q10)

Continual improvement:

Recurring activity to increase the ability to fulfill requirements. (ISO 9000:2005)

Control strategy:

A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Corrective action:

Action to eliminate the cause of a detected non-conformity or other undesirable situation. NOTE: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005)

Design space:

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. (ICH Q8)

Enabler:

A tool or process which provides the means to achieve an objective. (ICH Q10)

Feedback / Feed-forward:

Feedback: The modification or control of a process or system by its results or effects.

Feed-forward: The modification or control of a process using its anticipated results or effects. (Oxford Dictionary of English by Oxford University Press, 2003)

Feedback/ feed-forward can be applied technically in process control strategies and conceptually in quality management. (ICH Q10)

Innovation:

The introduction of new technologies or methodologies. (ICH Q10)

Knowledge management:

Systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components. (ICH Q10)

Outsourced activities:

Activities conducted by a contract acceptor under a written agreement with a contract giver. (ICH Q10)

Performance indicators:

Measurable values used to quantify quality objectives to reflect the performance of an organisation, process or system, also known as “performance metrics” in some regions. (ICH Q10)

Pharmaceutical Quality System (PQS):

Management system to direct and control a pharmaceutical company with regard to quality. (ICH Q10 based upon ISO 9000:2005)

Preventive action:

Action to eliminate the cause of a potential non-conformity or other undesirable potential situation.

NOTE: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. (ISO 9000:2005)

Product realisation:

Achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities (including compliance with marketing authorisation) and internal customers’ requirements. (ICH Q10)

Quality:

The degree to which a set of inherent properties of a product, system or process fulfils requirements. (ICH Q9)

Quality manual:

Document specifying the quality management system of an organisation. (ISO 9000:2005)

Quality Objectives:

A means to translate the quality policy and strategies into measurable activities. (ICH Q10)

Quality planning:

Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfill the quality objectives. (ISO 9000:2005)

Quality policy:

Overall intentions and direction of an organisation related to quality as formally expressed by senior management. (ISO 9000:2005)

Quality risk management:

A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. (ICH Q9)

Senior management:

Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilise resources within the company or site. (ICH Q10 based in part on ISO 9000:2005)

State of control:

A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)

Annex 1

Potential opportunities to enhance science and risk based regulatory approaches *

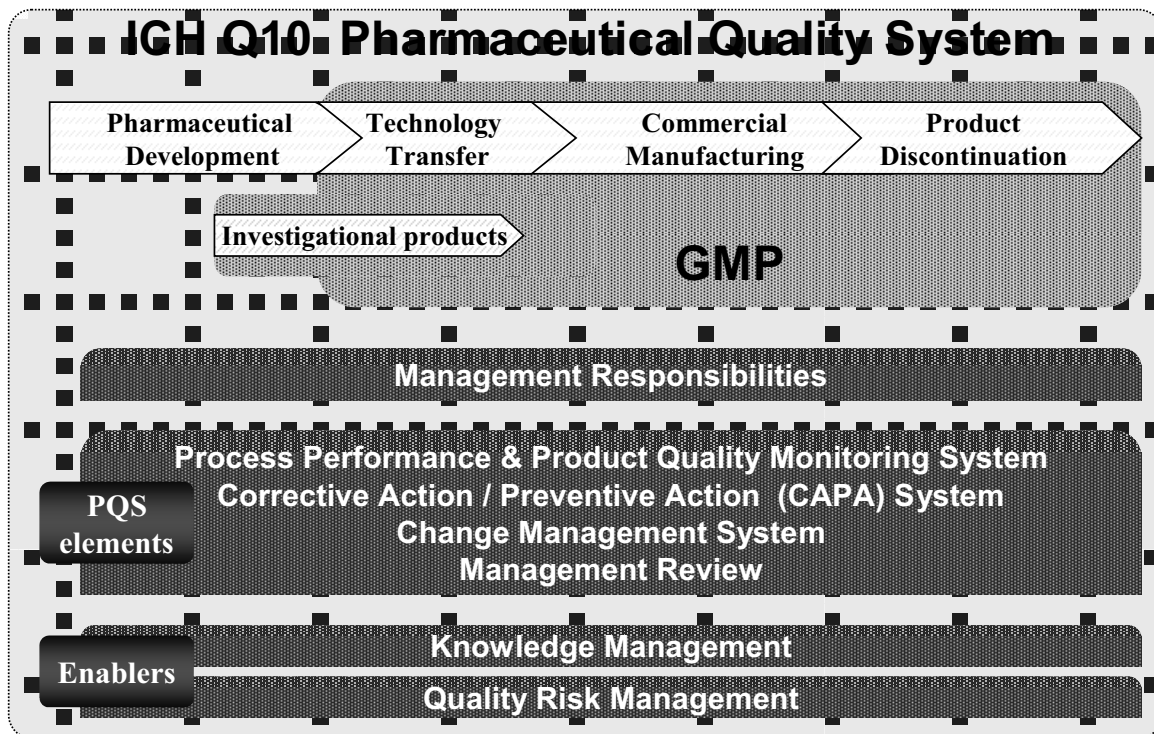
*Note: This annex reflects potential opportunities to enhance regulatory approaches. The actual regulatory process will be determined by region.

Scenario	Potential opportunity
1. Comply with GMPs	Compliance – status quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10).	Opportunity to: increase use of risk based approaches for regulatory inspections.
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	Opportunity to: - facilitate science based pharmaceutical quality assessment; - enable innovative approaches to process validation; - establish real-time release mechanisms.
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q10).	Opportunity to: - increase use of risk based approaches for regulatory inspections; - facilitate science based pharmaceutical quality assessment; - optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement; - enable innovative approaches to process validation; - establish real-time release mechanisms.

Annex 2

Annex 2

Diagram of the ICH Q10 Pharmaceutical Quality System Model



This diagram illustrates the major features of the ICH Q10 Pharmaceutical Quality System (PQS) model. The PQS covers the entire lifecycle of a product including pharmaceutical development, technology transfer, commercial manufacturing, and product discontinuation as illustrated by the upper portion of the diagram. The PQS augments regional GMPs as illustrated in the diagram. The diagram also illustrates that regional GMPs apply to the manufacture of investigational products.

The next horizontal bar illustrates the importance of management responsibilities explained in Section 2 to all stages of the product lifecycle. The following horizontal bar lists the PQS elements which serve as the major pillars under the PQS model. These elements should be applied appropriately and proportionally to each lifecycle stage recognising opportunities to identify areas for continual improvement.

The bottom set of horizontal bars illustrates the enablers: knowledge management and quality risk management, which are applicable throughout the lifecycle stages. These enablers support the PQS goals of achieving product realisation, establishing and maintaining a state of control, and facilitating continual improvement.



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Quality Risk Management (ICH Q9)

The ICH Q9 document on Quality Risk Management was adopted at step 4 at the ICH Steering Committee meeting on 9 November 2005.

Quality Risk Management can be applied not only in the manufacturing environment, but also in connection with pharmaceutical development and preparation of the quality part of marketing authorisation dossiers. The guideline applies also to the regulatory authorities in the fields of pharmaceutical assessment of the quality part of the marketing authorisation dossier, GMP inspections and the handling of suspected quality defects. Nevertheless for coherence the text was included within the GMP Guide as Annex 20 in March 2008. Since the creation of Part III of the GMP Guide it has been recognised that Part III is a more appropriate location for its publication.

As part of the EU implementation of ICH Q9, an amendment to Chapter 1 of the GMP Guide (Quality Management) was published in February 2008 which came into force in July 2008. This amendment incorporated the principles of Quality Risk Management into the Chapter.

The text of this document, formerly Annex 20, remains optional and provides examples of the processes and applications of Quality Risk Management.



Quality Risk Management (ICH Q9)

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1. Introduction

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of quality risk management in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of quality systems has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. However, achieving a shared understanding of the application of risk management among diverse stakeholders is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.

The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight.

The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk based decisions, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures e.g. standard operating procedures). The use of informal risk management processes (using empirical tools and/ or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.

Decision nodes are not shown in the diagram above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision. Note: "unacceptable" in the flowchart does not only refer to statutory, legislative or regulatory requirements, but also to the need to revisit the risk assessment process.

4.1. Responsibilities

Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g. quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical) in addition to individuals who are knowledgeable about the quality risk management process.

Decision makers should

- take responsibility for coordinating quality risk management across various functions and departments of their organization; and
- assure that a quality risk management process is defined, deployed and reviewed and that adequate resources are available.

4.2. Initiating a quality risk management process

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk
- Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment
- Identify a leader and necessary resources
- Specify a timeline, deliverables and appropriate level of decision making for the risk management process

4.3. Risk assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool (see examples in section 5) and the types of information needed to address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the “What might go wrong?” question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems.

The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as “high”, “medium”, or “low”, which should be defined in as much detail as possible. Sometimes a “risk score” is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

4.4. Risk control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 1). Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

4.5. Risk communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Fig. 1: dashed arrows). The output/result of the quality risk management process should be appropriately communicated and documented (see Fig. 1: solid arrows). Communications might include those among interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.

4.6. Risk review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g. results of product review, inspections, audits, change control) or unplanned (e.g. root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions (section 4.4).

5. Risk management methodology

Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk.

Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/ or internal procedures) based on, for example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources.

Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools (further details in Annex 1 and chapter 8):

- Basic risk management facilitation methods(flowcharts, check sheets etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug (medicinal) product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g. Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.

The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/ or criticality of the issue to be addressed.

6. Integration of quality risk management into industry and regulatory operations

Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems (see Annex II). As outlined in the introduction, appropriate use of quality risk management does not obviate industry's obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties.

Training of both industry and regulatory personnel in quality risk management processes provides for greater understanding of decision-making processes and builds confidence in quality risk management outcomes.

Quality risk management should be integrated into existing operations and documented appropriately. Annex II provides examples of situations in which the use of the quality risk management process might provide information that could then be used in a variety of pharmaceutical operations. These examples are provided for illustrative purposes only and should not be considered a definitive or exhaustive list. These examples are not intended to create any new expectations beyond the requirements laid out in the current regulations.

Examples for industry and regulatory operations (see Annex II):

- Quality management

Examples for industry operations and activities (see Annex II):

- Development
- Facility, equipment and utilities
- Materials management
- Production
- Laboratory control and stability testing
- Packaging and labelling

Examples for regulatory operations (see Annex II):

- Inspection and assessment activities

While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information. This collaboration could be important in the development of policies and guidelines that integrate and support quality risk management practices.

7. Definitions

Decision maker(s) – Person(s) with the competence and authority to make appropriate and timely quality risk management decisions

Detectability - the ability to discover or determine the existence, presence, or fact of a hazard

Harm – damage to health, including the damage that can occur from loss of product quality or availability

Hazard - the potential source of harm (ISO/IEC Guide 51)

Product Lifecycle – all phases in the life of the product from the initial development through marketing until the product's discontinuation

Quality – the degree to which a set of inherent properties of a product, system or process fulfills requirements (see ICH Q6a definition specifically for "quality" of drug substance and drug (medicinal) products.)

Quality risk management – a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle

Quality system – the sum of all aspects of a system that implements quality policy and ensures that quality objectives are met

Requirements – the explicit or implicit needs or expectations of the patients or their surrogates (e.g. health care professionals, regulators and legislators). In this document, "requirements" refers not only to statutory, legislative, or regulatory requirements, but also to such needs and expectations.

Risk – the combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51)

Risk acceptance – the decision to accept risk (ISO Guide 73)

Risk analysis – the estimation of the risk associated with the identified hazards

Risk assessment – a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk communication – the sharing of information about risk and risk management between the decision maker and other stakeholders

Risk control – actions implementing risk management decisions (ISO Guide 73)

Risk evaluation – the comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk

Risk identification – the systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description

Risk management – the systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk

Risk reduction – actions taken to lessen the probability of occurrence of harm and the severity of that harm

Risk review – review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk

Severity – a measure of the possible consequences of a hazard

Stakeholder – any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry

Trend – a statistical term referring to the direction or rate of change of a variable(s)

8. References

ICH Q8 Pharmaceutical development

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IEC 61882 - Hazard Operability Analysis (HAZOP)

ISO 14971:2000 - Application of Risk Management to Medical Devices

ISO 7870:1993 - Control Charts

ISO 7871:1997 - Cumulative Sum Charts

ISO 7966:1993 - Acceptance Control Charts

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Annex I: Risk management methods and tools

The purpose of this annex is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

I.1 Basic risk management facilitation methods

Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision-making are:

- Flowcharts
- Check Sheets
- Process Mapping
- Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram)

I.2 Failure Mode Effects Analysis (FMEA)

FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.

Potential areas of use(s)

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.

FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/ results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

I.3 Failure Mode, Effects and Criticality Analysis (FMECA)

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA; see IEC 60812). In order for such an analysis to be performed, the product or process specifications should be established. FMECA can identify places where additional preventive actions might be appropriate to minimize risks.

Potential areas of use(s)

FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes; however, it is not limited to this application. The output of an FMECA is a relative risk "score" for each failure mode, which is used to rank the modes on a relative risk basis.

I.4 Fault Tree Analysis (FTA)

The FTA tool (see IEC 61025) is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or sub-system) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts' process understanding to identify causal factors.

Potential areas of use(s)

FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e. solve one problem yet cause a different problem). Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.

I.5 Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety (see WHO Technical Report Series No 908, 2003 Annex 7). It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

HACCP consists of the following seven steps:

- (1) conduct a hazard analysis and identify preventive measures for each step of the process;
- (2) determine the critical control points;
- (3) establish critical limits;
- (4) establish a system to monitor the critical control points;
- (5) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control;
- (6) establish system to verify that the HACCP system is working effectively;
- (7) establish a record-keeping system.

Potential areas of use(s)

HACCP might be used to identify and manage risks associated with physical, chemical and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.

I.6 Hazard Operability Analysis (HAZOP)

HAZOP (see IEC 61882) is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called "guide-words". "Guide-words" (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. It often uses a team of people with expertise covering the design of the process or product and its application.

Potential areas of use(s)

HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug (medicinal) products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

I.7 Preliminary Hazard Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system. The tool consists of: 1) the identification of the possibilities that the risk event happens, 2) the qualitative evaluation of the extent of possible injury or damage to health that could result and 3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and 4) the identification of possible remedial measures

Potential areas of use(s)

PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.

I.8 Risk ranking and filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential areas of use(s)

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful when management needs to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.

I.9 Supporting statistical tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:

- Control charts, for example:
 - Acceptance control charts (see ISO 7966)
 - Control charts with arithmetic average and warning limits (see ISO 7873)
 - Cumulative sum charts (see ISO 7871)
 - Shewhart control charts (see ISO 8258)
 - Weighted moving average
- Design of Experiments (DOE)
- Histograms
- Pareto charts
- Process capability analysis

Annex II: Potential applications for quality risk management

This annex is intended to identify potential uses of quality risk management principles and tools by industry and regulators. However, the selection of particular risk management tools is completely dependent upon specific facts and circumstances.

These examples are provided for illustrative purposes and only suggest potential uses of quality risk management. This Annex is not intended to create any new expectations beyond the current regulatory requirements.

II.1 Quality risk management as part of integrated quality management

Documentation

To review current interpretations and application of regulatory expectations

To determine the desirability of and/or develop the content for SOPs, guidelines, etc.

Training and education

To determine the appropriateness of initial and/or ongoing training sessions based on education, experience and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness)

To identify the training, experience, qualifications and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product

Quality defects

To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc.

To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall)

Auditing / Inspection

To define the frequency and scope of audits, both internal and external, taking into account factors such as:

- Existing legal requirements
- Overall compliance status and history of the company or facility
- Robustness of a company's quality risk management activities
- Complexity of the site
- Complexity of the manufacturing process
- Complexity of the product and its therapeutic significance
- Number and significance of quality defects (e.g, recall)
- Results of previous audits/inspections
- Major changes of building, equipment, processes, key personnel
- Experience with manufacturing of a product (e.g. frequency, volume, number of batches)
- Test results of official control laboratories

Periodic review

To select, evaluate and interpret trend results of data within the product quality review

To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling)

Change management / Change control

To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing

To evaluate the impact of the changes on the availability of the final product

To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers

To determine appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation or communication with regulators

Continual improvement

To facilitate continual improvement in processes throughout the product lifecycle.

II.2 Quality risk management as part of regulatory operations

Inspection and assessment activities

To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity (see "Auditing" section in Annex II.1)

To evaluate the significance of, for example, quality defects, potential recalls and inspectional findings

To determine the appropriateness and type of post-inspection regulatory follow-up

To evaluate information submitted by industry including pharmaceutical development information

To evaluate impact of proposed variations or changes

To identify risks which should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled (e.g., parametric release, Process Analytical Technology (PAT)).

II.3 Quality risk management as part of development

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8)

To enhance knowledge of product performance over a wide range of material attributes (e.g. particle size distribution, moisture content, flow properties), processing options and process parameters

To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials

To establish appropriate specifications, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing)

To decrease variability of quality attributes:

- reduce product and material defects
- reduce manufacturing defects

To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer

To make use of the "design space" concept (see ICH Q8)

II.4 Quality risk management for facilities, equipment and utilities

Design of facility / Equipment

To determine appropriate zones when designing buildings and facilities, e.g.,

- flow of material and personnel
- minimize contamination
- pest control measures

- prevention of mix-ups
- open versus closed equipment
- clean rooms versus isolator technologies
- dedicated or segregated facilities / equipment

To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants)

To determine appropriate utilities (e.g., steam, gases, power source, compressed air, heating, ventilation and air conditioning (HVAC), water)

To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts)

Hygiene aspects in facilities

To protect the product from environmental hazards, including chemical, microbiological, and physical hazards (e.g., determining appropriate clothing and gowning, hygiene concerns)

To protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured

Qualification of facility / Equipment / Utilities

To determine the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods)

Cleaning of equipment and environmental control

To differentiate efforts and decisions based on the intended use (e.g., multi- versus single-purpose, batch versus continuous production)

To determine acceptable (specified) cleaning validation limits

Calibration / Preventive maintenance

To set appropriate calibration and maintenance schedules

Computer systems and computer controlled equipment

To select the design of computer hardware and software (e.g., modular, structured, fault tolerance)

To determine the extent of validation, e.g..

- identification of critical performance parameters
- selection of the requirements and design
- code review
- the extent of testing and test methods
- reliability of electronic records and signatures

II.5 Quality risk management as part of materials management

Assessment and evaluation of suppliers and contract manufacturers

To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements)

Starting material

To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).

Use of materials

To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing)

To determine appropriateness of reprocessing, reworking, use of returned goods

Storage, logistics and distribution conditions

To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design)

To determine the effect on product quality of discrepancies in storage or transport conditions (e.g. cold chain management) in conjunction with other ICH guidelines

To maintain infrastructure (e.g. capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance)

To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

II.6 Quality risk management as part of production

Validation

To identify the scope and extent of verification, qualification and validation activities (e.g., analytical methods, processes, equipment and cleaning methods)

To determine the extent for follow-up activities (e.g., sampling, monitoring and re-validation)

To distinguish between critical and non-critical process steps to facilitate design of a validation study

In-process sampling & testing

To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control)

To evaluate and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release

Production planning

To determine appropriate production planning (e.g., dedicated, campaign and concurrent production process sequences).

II.7 Quality risk management as part of laboratory control and stability studies

Out of specification results

To identify potential root causes and corrective actions during the investigation of out of specification results

Retest period / Expiration date

To evaluate adequacy of storage and testing of intermediates, excipients and starting materials

II.8 Quality risk management as part of packaging and labelling

Design of packages

To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility)

Selection of container closure system

To determine the critical parameters of the container closure system

Label controls

To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Forty-fourth report



World Health
Organization

The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications.

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Forty-fourth report



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Geneva, 12–16 October 2009

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Professor Saleh A. Bawazir, Professor Theo G. Dekker, Ms Nilka M. Guerrero Rivas, Professor Jos Hoogmartens, Professor Jin Shaohong, Dr John H. McB. Miller, Dr Justina A. Molzon and Mr Eshetu Wondemagegnehu Biwota reported no conflict of interest.

Temporary and special advisers reported the following:

Professor Ivan Addae-Mensah, Dr Simon Mills, Ms Marie-Louise Rabouhans, Dr Birgit Schmauser, Dr Saranjit Singh and Mr Deryck Smith, reported no conflict of interest.

Mr Robert Tribe reported that he was a consultant with two commercial entities and was the owner of another one.

Mr Martin FitzGerald, attending as an observer, reported that he was Legal Adviser with the European Association of Pharmaceutical Full-Line Wholesalers; Dr Piotr Kozarewicz (representative of the European Medicines Agency) reported that he was employed by two different pharmaceutical companies in Poland from September 2003 until June 2006. Other participants reported no conflict of interest.

1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 12 to 16 October 2009. Dr Carissa F. Etienne, Assistant Director-General, Health Systems and Services (HSS), opened the meeting and, on behalf of the Director-General of the World Health Organization, welcomed all the participants to the forty-fourth meeting. She expressed her appreciation of the Expert Committee for its knowledge of and expertise in the work of WHO in the area of quality assurance of medicines. Dr Etienne welcomed the members of the Committee, temporary advisers and special advisers for prequalification; representatives of the United Nations Children's Fund, the Global Fund to Fight AIDS, Tuberculosis and Malaria, Council of Europe/European Directorate for the Quality of Medicines and HealthCare, European Medicines Agency, International Federation of Pharmaceutical Manufacturers and Associations, International Generic Pharmaceutical Alliance, International Pharmaceutical Excipients Council, International Pharmaceutical Federation, World Self-Medication Industry and an observer from the European Association of Pharmaceutical Full-line Wholesalers; representatives of the Secretariats of the Pharmacopoeias of Republic of Korea and United States of America; as well as representatives from WHO Collaborating Centres in China and South Africa.

She said the WHO Member States and the world's political and international health leaders recognized the need to strengthen health systems, renew political interest in making sustainable improvements that benefited disease areas and health programmes, and to redouble global efforts to meet the challenge of achieving the Millennium Development Goals and renew primary health care systems. Dr Etienne said that health systems had to respond better and faster to the challenges of the changing world. She stressed the single framework for action with six building blocks (governance and leadership; financing; information; medical products, vaccines and technologies; health workforce; and service delivery); health systems and health outcome programmes; obtaining results; and a more effective role for WHO at country level.

Medicines were an important component of the health system; however, unavailability, costliness and lack of quality, including counterfeit medicines, were issues of concern to countries. Developing countries with these problems were accepting policy and regulatory change as well as enforcing laws and regulations to improve availability.

The work of this Expert Committee was important to WHO Member States, United Nations and international organizations, and also in-house for all programmes dealing with medicines. One example was the Prequalification Programme (PQP) which was based entirely on the

implementation of guidelines and standards recommended by the Expert Committee on Specifications for Pharmaceutical Preparations. The work of the Expert Committee was closely linked to other organizations, for example, the European Medicines Agency, European Directorate for the Quality of Medicines and HealthCare, the Global Fund to Fight AIDS, Tuberculosis and Malaria, International Atomic Energy Agency, United Nations Children's Fund, World Intellectual Property Organization, World Bank, International Pharmaceutical Federation, International Federation of Pharmaceutical Manufacturers and Associations, World Self-Medication Industry, national and regional pharmacopoeias, other clusters, institutions, bodies, authorities, and other WHO Expert Committees.

Experts and the Secretariat were committed to this important work enabling quality medicines to reach patients. Dr Etienne raised the issue of counterfeit medicines, which should be addressed as a public health problem. Discussion during the Executive Board meeting in January 2009 regarding the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) and counterfeit medicines issues in general raised concerns regarding WHO's role in this area. (For a further update see section 2.3.)

Dr Gilles Forte, speaking on behalf of the Director, Essential Medicines and Pharmaceutical Policies (EMP), expressed the importance of the Committee's work on standard-setting for the functionality of good manufacturing practices (GMP); he also emphasized that the improvement of quality assurance, updating of quality guidelines and laboratory testing were key functions of the Committee. Dr Forte also acknowledged that the agenda was very impressive and thanked the Expert Committee for its support in helping define and address future challenges. He emphasized that WHO valued the work carried out by this Expert Committee.

Dr Lembit Rägo, Coordinator of the Quality Assurance and Safety: Medicines team, said that nowadays funding for the team mainly originated from external donors in order to sustain its activities, comprising those of this Expert Committee. The team, including the Medicines Quality Assurance Programme, must continue to attract donors and to date it had been relatively successful in obtaining donor funding.

A current challenge was related to the fact that a WHO Collaborating Centre had closed due to restructuring in Sweden, but the Programme was very hopeful that it could obtain a replacement institute quickly.

Dr Rägo informed the Committee that the Medicines Strategy was in print following the usual consultative process. It would be put on the web site for the next biennium with a link to the Millennium Development Goals.

Dr Rågo thanked the members of the Expert Committee for their dedication and contribution to the work of WHO, and also for the help and time given.

The Secretary of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Dr Sabine Kopp, explained the administrative process of appointment of experts and the working procedures related to the Expert Committee meeting.

The Secretary explained that the Expert Committee was an official advisory body to the Director-General of WHO and was governed through rules and procedures. The report of the WHO Expert Committee consisted of a summary of the discussions, recommendations to WHO and its Member States and included newly adopted guidelines. The report was presented to the WHO Governing Bodies for final comments, endorsement and implementation by Member States and constituted WHO technical guidance.

The Expert Committee consultation process involves several steps, i.e. preliminary consultation and drafting, circulation of the first draft for comments, revision of the draft, discussion of the draft by the WHO Expert Committee and finally, once adopted, publication in the Expert Committee report as an annex, submission to the WHO Governing Bodies and recommendation to Member States for implementation.

2. General policy

2.1 International collaboration

2.1.1 *International organizations, agencies and nongovernmental organizations*

The Expert Committee welcomed the collaboration of international organizations and agencies with the work of this Committee. The following presented their work in more detail.

European Directorate for the Quality of Medicines and HealthCare

The European Directorate for the Quality of Medicines and HealthCare (EDQM) is responsible for a number of activities in collaboration with the European Union, related to surveillance of pharmaceutical products marketed and distributed in Europe. EDQM is at the centre of the European regulatory framework for medicines and one of its tasks since 2008 has been to protect patients in Europe from counterfeit medicines. Another activity transferred to EDQM in 2008 is the legal classification of medicines as regards their supply with or without medical prescription. Since 2009 EDQM activities have expanded to include newer areas, e.g. cosmetics and food contact materials, packaging and containers. EDQM collaborates in

various WHO activities, including the joint EDQM/WHO External Quality Assurance Assessment Scheme.

European Medicines Agency

The European Medicines Agency (EMA) works under the European Union (EU) regulatory system and protects and promotes public and animal health, facilitates access for patients to new and better medicines, coordinates the safety of medicines (pharmacovigilance), procures the same product information for professionals and for patients, promotes the European pharmaceutical industry and is a platform for public health issues at the European level.

The role of EMA in the regulation of human and veterinarian medicines covers: designation of orphan medicines; paediatric investigation plans; scientific advice; initial application; post-authorization; referrals from national authorization systems; inspection (coordination and guidelines); information; parallel import and certificate; guidelines; advice and support to EU commissions, the EU parliament and Member States.

The Global Fund to Fight AIDS, Tuberculosis and Malaria

In November 2007, during the sixteenth Board Meeting of the Global Fund, the Board requested the Secretariat to carry out a review of the quality assurance (QA) Policy for Pharmaceutical Products under oversight of the Portfolio Committee. In November 2008 the Board approved a revised QA policy.

As a general rule the Global Fund will only fund the purchase of finished pharmaceutical products (FPPs) that are either WHO-prequalified or stringent regulatory authority (SRA)-authorized. This would provide an improved economic incentive for the manufacturers of FPPs to conform to these standards. It should also limit opportunistic strategies adopted by suppliers who might initiate a process of prequalification but who do not take the necessary steps to effectively pursue it until its end.

Groupement International de la Répartition Pharmaceutique — European Association of Pharmaceutical Full-line Wholesalers

The representative of the European Association of Pharmaceutical Full-line Wholesalers gave a brief update on the Association's activities and involvement in the development of good distribution practices for pharmaceutical products (see section 8.2). He also gave the view and feedback from the Healthcare Distribution Management Association (HDMA) especially regarding good distribution practices. The representative indicated that there was a need to clearly identify and define the activities of all participants in the supply chain, including those of the holders of a marketing authorization and the holders of a distribution authorization, as

well as for those parties involved in the supply to the public that did not physically handle medicines. It was important to allocate responsibilities to all participants, to license and inspect all actors in accordance with the relevant good practices, such as GMP, good distribution practices, good trade practices and good brokerage practice.

International Federation of Pharmaceutical Manufacturers and Associations

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) had official observer status with the United Nations in Geneva, including WHO. IFPMA represents the research-based pharmaceutical, biotechnological and vaccine industry, and global intergovernmental agencies. It advocates policies that encourage discovery of new life-saving and life-enhancing medicines.

IFPMA supports high standards of manufacturing and quality assurance in two areas:

- vaccines and biotechnology products, working in collaboration with WHO/EMP and the WHO Expert Committee on Biological Standardization; and
- medicines, including medicines for children, in collaboration with this Expert Committee and the WHO Expert Committee on the Selection and Use of Essential Medicines.

International Generic Pharmaceutical Alliance

The International Generic Pharmaceutical Alliance (IGPA) has member generic trade associations from Canada, Europe, India, Japan and the USA. Observer status had been granted within the last year to generic associations from Brazil, the People's Republic of China, Jordan and South Africa; observer status for Malaysia and Mexico was currently under consideration. The General Policy Initiatives of IGPA comprise cross-cutting quality assurance issues, collaboration with the WHO Expert Committee on Biological Standardization and International Collaboration (ICH Expert Working Groups on Quality and Safety). Other activities supported by IGPA are:

- nomenclature, terminology and databases — IGPA and the European Generic Medicines Association (EGA) have been involved in the discussion of international nonproprietary names (INN) for biologicals and biosimilars;
- prequalification of priority essential medicines — EGA works with WHO on an accelerated prequalification procedure for generics approved by SRAs;
- bioequivalence — although not on the WHO Expert Committee's agenda, IGPA was working on a proposal for international harmonization of bioequivalence requirements; and

— stability — IGPA was working with certain national associations regarding implementation of the latest WHO stability guidelines.

International Pharmaceutical Federation

The International Pharmaceutical Federation (FIP) reported that over the past year FIP and WHO had established work plans to support their involvement in key strategic collaborative areas of work. FIP's main priority was medicines and strengthening the pharmaceutical workforce. Other areas of importance included the roles and added value of pharmacists in patient safety, primary health care, noncommunicable diseases and maternal, newborn and child health. FIP continued to collaborate on these projects related to medicines in WHO.

In particular the issue of good distribution practices (GDP) is an important element in securing the legitimate supply and distribution chain, and also in preventing the infiltration of counterfeit medical products (see section 8.2). FIP played an active role in the final revision and drafting of the WHO GDP guidelines in September 2009. FIP had produced a WHO/FIP Handbook on Developing Pharmacy Practice and is currently working towards a revision of the FIP/WHO guidelines on good pharmacy practice (GPP). FIP also assisted IMPACT in improving the information available to the public regarding counterfeit medicines and the work of IMPACT.

United Nations Children's Fund

The United Nations Children's Fund (UNICEF) promotes and protects children's rights, especially those of the most vulnerable in the poorest countries. UNICEF core commitments are health and nutrition, education, water and sanitation, child protection and HIV/AIDS.

One of the main activities of UNICEF is the supply of quality medicines to countries and communities in need; the supply headquarters is located in Copenhagen. The Supply Division oversees UNICEF's global supply procurement and logistics operations on behalf of UNICEF and its procurement services partners. It ensures that supplies of high quality and good value reach children and their families quickly.

Prequalification of suppliers of pharmaceuticals in UNICEF involves the review of submitted documentation and/or GMP inspections to ensure compliance with WHO GMP guidelines using a technical questionnaire developed by WHO. The technical questionnaire covers manufacturing sites, dosage forms and products of interest, export experience and licence to manufacture pharmaceuticals. Local authorities are invited to participate in GMP inspections. There are also joint inspections with WHO and other partners.

Decisions are based on the regulatory environment in the country of origin and prior experience of UNICEF, GMP inspection by UNICEF or by a

representative selected by UNICEF. Contract manufacture is only accepted if the subcontractor is also approved by UNICEF. Inspections are carried out primarily by UNICEF staff who check compliance with WHO GMP guidelines. During 2003–2009, 145 GMP inspections carried out in 47 companies failed (32%). In case of failure a detailed GMP inspection report is forwarded to the company with a request to respond within one month.

In case of prequalification of vaccines, HIV, malaria and tuberculosis products:

- products have to be prequalified by WHO and listed on the WHO web site;
- the supplier has to confirm to UNICEF that the products are identical to those assessed by WHO/UNICEF; and
- UNICEF's purchase is traced in WHO/UNICEF GMP inspections.

2.1.2 **Pharmacopoeial Discussion Group**

The Pharmacopoeial Discussion Group (PDG), which consists of the European Pharmacopoeia, Japanese Pharmacopoeia and United States Pharmacopoeia, met in association with the Expert Working Groups of the International Conference on Harmonisation (ICH) from 8 to 12 June 2009 in Yokohama, Japan. The Secretary of this Expert Committee participated as an observer for WHO.

The experts recommended reviews of the following general methods against existing related *International Pharmacopoeia* (Ph.Int.) texts and adding those not yet included in the Ph.Int. for future adoption:

- Test for extractable volume of parenteral preparations (General Chapter);
- Test for particulate contamination: sub-visible particles (General Chapter);
- Disintegration test;
- Dissolution test (General Chapter) (pending availability of final text);
- Sterility test (General Chapter);
- Microbiological examination of non-sterile products; and
- Acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use (General Chapter).

The Committee recommended that the following should be considered for adoption:

- Microbiological examination of non-sterile products:
 - Microbial enumeration tests (General Chapter);
 - Tests for specified microorganisms (General Chapter); and
- Tablet friability (General Chapter).

The Secretariat informed the experts that preliminary discussions had already been held with the PDG members, based on previous recommendations

of the Expert Committee. The PDG parties indicated that, in the event of these methods being of interest to *The International Pharmacopoeia*, WHO should contact the respective PDG Lead Pharmacopoeias regarding their final acceptance to use the texts within the Ph.Int.

2.1.3 *International Conference on Harmonisation*

The International Conference on Harmonisation (ICH) Expert Working Groups met from 8 to 12 June 2009 in Yokohama, Japan.

The Secretary of this Expert Committee also attended, as an observer for WHO, the ICH Q4B Working Group meetings (consisting of members from the six ICH partners and observers). An update of the current activities in the quality area was given by the co-chair of the meeting.

2.1.4 *International Conference of Drug Regulatory Authorities*

The International Conference of Drug Regulatory Authorities (ICDRA) provide medicines regulatory authorities (MRAs) of WHO Member States with a forum to meet and discuss ways to strengthen collaboration. The conferences have been held since 1980 with the aim of promoting exchange of information and collaborative approaches to issues of common concern. As a platform established to develop international consensus, the ICDRA continues to be an important tool for WHO and MRAs in their efforts to harmonize regulation and improve the safety, efficacy and quality of medicines. The ICDRA programme is developed by a planning committee of representative medicines regulators. Discussions during the four days of the ICDRA usually include topics relating to quality issues, herbal medicines, homeopathy, regulatory reform, medicines safety, counterfeiting, access, regulation of clinical trials, harmonization, new technologies and e-commerce. Recommendations are proposed for action among agencies, WHO and related institutions.

The recommendations formulated by the 13th International Conference of Drug Regulatory Authorities held in Berne, Switzerland, from 16 to 19 September 2008 are available on the WHO web site (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra).

The 14th ICDRA would take place in Singapore from 30 November to 3 December 2010. A pre-ICDRA meeting on “Effective Collaboration: The Future for Medicines Regulation” would take place on 28–29 November.

Registration, details and programme are available on the ICDRA web site: <http://www.icdra2010.sg/>.

2.2 Cross-cutting issues in pharmaceuticals — quality assurance issues

2.2.1 *Herbal medicines*

The Committee received a report on WHO's policy and activities in the field of traditional medicine.

The representative of the Traditional Medicine (TRM) team reported on the activities of International Regulatory Cooperation for Herbal Medicines (IRCH) — membership had increased to 22, consisting of 19 Member Countries and three Member Regional Bodies. The third annual meeting was held in Montreal, Canada in February 2009, at which a strategic plan of action for IRCH was discussed and agreed upon. Based on the review of current issues relating to herbal medicines, eight working groups addressing the priority issues identified had been established.

TRM also reported on the publication of Volume 4, *WHO monographs on selected medicinal plants*, which contained 28 monographs. TRM thanked the Expert Committee and the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations for their technical contribution and support in the development of the monographs.

A major outcome of the WHO Congress on Traditional Medicine was the adoption of the “Beijing Declaration”. The World Health Assembly in May 2009 adopted a new resolution on traditional medicine (resolution WHA 62.13), referring to the “Beijing Declaration” and requested the Director-General to update the WHO Traditional Medicine Strategy. It also requested WHO to support the efforts of Member States in integrating traditional medicine into national health systems.

In the context of primary health care, the report of the WHO interregional workshop on the use of traditional medicine in primary health care, held in Ulaanbaatar, Mongolia in August 2007, was printed in May 2009 and was widely disseminated.

The Committee was informed of WHO's new project on the development of international classification of traditional medicine, towards the integration of traditional medicine into general health information systems, and standardization of clinical terms used by providers of traditional medicine. This project also aimed at responding to the need expressed by national pharmacovigilance centres for an appropriate coding system accommodating the reporting of adverse events to herbal medicines.

The Committee was also informed about the progress of implementation of the Global Strategy and Plan of Action on public health, innovation and intellectual property (GSPOA) in the field of traditional medicine.

The Expert Committee encouraged countries to make use of the materials available from this Programme and took note of the role of traditional medicines within the concept of primary health care.

2.2.2 *Biologicals and vaccines*

WHO Expert Committee on Biological Standardization

The role of the Expert Committee on Biological Standardization was to develop international recommendations for the production and control of biological medicines and the establishment of associated international biological reference materials. The Committee would next meet on 19–23 October 2009 and a key agenda item that might be of interest to the Expert Committee on Specifications for Pharmaceutical Preparations was the proposed guidelines on evaluation of similar biotherapeutic products. These guidelines, if established, would set international expectations for the regulatory evaluation of this increasingly important and relatively new class of biological medicines. It would, however, be only a first stage in providing equity of access to this type of product and WHO recognized that much would need to be done to assist Member States to develop the capacity to ensure effective use of such products.

A second topic was the issue of transition of some drugs from biologicals to chemicals. The Expert Committee on Biological Standardization had initiated a process whereby all proposals for new or replacement reference materials were first submitted to the Committee for review. Proposals were being received for certain reference materials to be calibrated in SI units instead of the International Unit of biological activity. Where this was the case, consultation with the Expert Committee on Specifications for Pharmaceutical Preparations was also sought prior to the initiation of the study.

Two other topics for more detailed discussion by the Expert Committee on Specifications for Pharmaceutical Preparations were examples of cross-cutting initiatives between the two Committees. The first was the guidelines that were under development to establish GMP for blood establishments and the second, the guidelines for regulatory oversight of temperature-controlled distribution of pharmaceuticals.

A joint concern of both Committees was to ensure effective implementation of guidelines and recommendations. Implementation workshops had been set up by the secretariat to promote the understanding and use of guidelines and recommendations established by the Expert Committee on Biological Standardization. New guidelines on regulatory expectations for stability evaluation of vaccines had been used as a case study and positive feedback had been obtained from all stakeholders on the value of such an approach.

Finally, a review of the roles and responsibilities of the Expert Committee on Biological Standardization was proposed. It was approximately 10 years since the last such review and thus it was important to have such an external validation of the direction and output of the Committee. As part of the process comments from the Expert Committee on Specifications for Pharmaceutical Preparations would be invited.

2.2.3 **Blood products**

The Committee was informed about WHO's work in the area of blood products and related biologicals. More details on the GMP for blood establishments can be found in section 6.6.

2.2.4 **Essential medicines**

Further to the WHO-led initiative "make medicines child size" launched in December 2007, WHO received a grant from the Bill & Melinda Gates Foundation in October 2008 to work in collaboration with UNICEF in order to conduct crucial research in the area of children's medicines. The aim of the project was to increase the number of child-size medicines designed and formulated specifically for children. The grant provided support for essential research to:

- determine the optimum dosage forms for paediatric medicines (e.g. small tablets, dispersible tablets, powders);
- develop dosing guides (e.g. a review of existing priority medicines and the identification of the appropriate doses for new medicines for children); and
- develop guidelines for testing of medicines and treatment of use of medicines in children, including guidelines on conducting clinical trials in children.

In December 2008 a group of paediatricians, pharmacists, clinical pharmacologists and representatives of the European Medicines Agency (EMA), International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Medicines for Malaria Venture (MMV), National Institutes of Health (NIH), United Nations Children's Fund (UNICEF) and the Bill & Melinda Gates Foundation attended a meeting hosted by WHO to discuss the preferred dosage form of medicines for children. As a result of this consultation the dosage forms of medicines most suitable for children were identified, with particular attention paid to conditions prevailing in developing countries and future areas of research required in this area (http://www.who.int/childmedicines/progress/Dosage_form_reportDEC2008.pdf).

The report of the WHO Subcommittee for the Selection and Use of Medicines, including the second Essential Medicines List for Children (EMLc), was reviewed and endorsed by the Expert Committee on Selection

and Use of Essential Medicines at its seventeenth meeting in March 2009. New additions to the EMLc included sections on palliative care medicines; ear, nose and throat medicines and medicines for neonates, and also the inclusion of liposomal amphotericin B, a dispersible formulation of artemether + lumefantrine (20 mg + 120 mg) and enalapril tablets (2.5 mg and 5 mg). The Expert Committee agreed that the Subcommittee had fulfilled the terms of reference regarding the development and revision of the WHO EMLc and made the recommendation to the Executive Board and the Director-General that the Subcommittee should now be dissolved. However, it was recommended that future Expert Committees should include adequate expertise to consider medicines for children and maintain the EMLc.

The Expert Committee for the Selection and Use of Essential Medicines also reviewed simulation studies proposing potential new strengths for fixed-dose combinations (FDCs) of antituberculosis medicines for children: isoniazid 150 mg + pyrazinamide 400 mg + rifampicin 250 mg and ethambutol 250 mg + isoniazid 150 mg + pyrazinamide 400 mg + rifampicin 250 mg.

However, it was noted that at this time there were no FDCs that delivered the ideal doses of first-line medicines for tuberculosis treatment in children with weights between 5 and 30 kg. It was also highlighted that there was a need for a two-drug FDC for use in the continuation phase of treatment and the Expert Committee for the Selection and Use of Essential Medicines recommended that the following combination (for continuation treatment only) would be reasonable based on the analyses presented: isoniazid 150 mg + rifampicin 250 mg.

The Expert Committee for the Selection and Use of Essential Medicines reviewed and agreed a proposal by the Medicines Quality Assurance Programme for a revision to the listing of pharmaceutical products in the Model Lists of Essential Medicines. As a result, the medicines listed in the left-hand column would in future be named as the active moieties, using INN and, where applicable, entries in the right-hand column would provide information on the dosage forms and strengths of products available in WHO Member States. The explanatory notes in the Model List of Essential Medicines and the EMLc had also been expanded to provide more information and guidance to users with regard to dosage form terminology and medicine strength (see section 11.1).

Future activities in relation to the Better Medicines for Children project would include a summit in Amsterdam in October 2009 to discuss scientific standards required for undertaking clinical research in children. As part of this meeting WHO would host a discussion day with a group of experts from developing countries to identify what might need to be done to

adapt current guidance documents for promoting appropriate research on medicines for children in resource-poor settings. In February 2010 WHO would host a meeting of regulatory authorities to facilitate the development of a Paediatric Medicines Regulators Network.

2.2.5 Regulatory support

The Expert Committee was updated on the area of medicines regulatory support. The mission of QSM in medicines regulatory support was to enhance the capacity of national and regional medicines regulatory systems to contribute to universal access to medicines of assured safety, quality and efficacy. Core functions included developing evidence on the situation and needs of medicines regulatory systems worldwide; providing direct support to countries and regions for strengthening medicines regulation; developing and continuously improving tools to assist regulatory activities (e.g. guidelines, manuals and other information materials); facilitating communication and promoting harmonization among MRAs; developing and continuously improving internal capacities; and developing and maintaining comprehensive databases on MRAs.

The scope of regulatory support activities involved assessing medicines regulatory systems to identify needs, assisting in the development of institutional plans and supporting capacity building. So far, 50 assessments had been performed on 46 regulatory systems with the involvement of the respective WHO regional offices.

In close collaboration with the capacity building teams of the WHO Prequalification Programme and the WHO Immunization, Vaccines and Biologicals Department, the Medicines Regulatory Support Programme had organized various training activities to strengthen capacity of national MRAs.

Regional support involved provision of technical assistance to Regional Economic Communities in Africa, within the framework of the African Medicines Registration Harmonization Initiative.

The Medicines Regulatory Support Programme had been particularly active in promoting the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce; in facilitating harmonization of regulatory requirements with subregional economic blocs; and improving communication among MRAs through networking, sharing of information and regulatory decisions.

The Programme had also been active in providing feedback on the implementation of existing WHO guidelines, developing training materials, developing internal procedures, developing and maintaining technical competence of regulatory staff and enhancing technical cooperation with partners both within and outside the Organization.

Future work would include improving feedback and identification of needs for guidance, establishing a pool of regulatory experts and conducting the assessment of medicines regulatory systems in a more systematic way and for training purposes. The programme intends to establish a network of centres of excellence in the regulatory affairs area to serve as training centres, design new intervention mechanisms for supporting activities and new concepts for conducting day-to-day work.

2.2.6 *HIV-related activities*

The representative of the HIV Department, Strategic Information and Research Unit, gave a short update on how the work of this Expert Committee was useful to the HIV Department's activities. The Department published an annual report entitled "Towards universal access" on progress made in the health sector to address the HIV epidemic. In the section on access to treatment, it reported on the progress made on prequalification of antiretrovirals by QSM. A QSM quality assessment survey was also included in the 2008 report.

2.3 Counterfeit medicines

The Committee was provided with an update by the Programme Manager of the newly created EMP/QSM Anti-Counterfeiting Programme (ACM), who was also Executive Secretary ad interim of the IMPACT Secretariat.

Discussion took place during the Executive Board meeting in January 2009 on IMPACT and counterfeit medicines in general. Concerns had been raised regarding WHO's role in this area. Two background papers had been prepared by the WHO Secretariat and submitted to the World Health Assembly (one on the activities of IMPACT and the second on WHO's activities in the area of counterfeit (http://apps.who.int/gb/e/e_wha62.html, WHA62: **A62/13** Counterfeit medical products, and **A62/14** Counterfeit medical products: International Medical Products Anti-Counterfeiting Taskforce). Additional information on IMPACT could be found on the web site (<http://www.who.int/impact>). The Assembly agenda item on counterfeits was subsequently postponed to 2010.

The Secretariat and Chair for IMPACT continued to be based in WHO.

The Director-General of WHO reconfirmed that counterfeit medicines were an important issue for the Organization and that WHO would continue to collaborate with partners in this field. The WHO Secretariat would work on the basis that there were no changes to this current situation at least until the World Health Assembly in May 2010, during which WHO's role should be clarified by its Member States.

ACM would complete the following activities in 2009:

- Revise and update the WHO and IMPACT web sites.

- Proceed with the joint WHO Expert Committee on Specifications for Pharmaceutical Preparations/IMPACT review of the *WHO Good distribution practices (GDP) for pharmaceutical products*, which was proposed by IMPACT in 2007.
- Start the review process of the draft document on Model Legislation developed by IMPACT in 2008, including a revision of the current definition of counterfeit medicines, possibly through the Expert Committee.
- Plan and implement advocacy, training, country support and enforcement activities with interested governments in Africa, as far as specified donor funds were available (mostly from the European Union for African, Caribbean and Pacific countries).
- Recruit one technical expert on regulatory matters and pursue the possibility of FIP arranging the secondment of a communication expert.
- Prepare a fund-raising plan for future staff and activities to combat counterfeit medicines and approach interested donors.

In addition to WHO's work on counterfeit medicines described above, the Assistant Director-General, HSS would continue her two-year mandate as elected Chair of IMPACT and WHO would continue to fulfil the functions of the IMPACT Secretariat. As such WHO would continue to work with IMPACT, drawing on its technical input and the involvement of a large number of stakeholders, whilst clearly distinguishing between documents prepared by IMPACT and those issued by WHO.

Technical documents prepared by IMPACT working groups would be posted on the IMPACT web site, without the WHO logo. These could be reviewed, adapted and ultimately approved as appropriate, through the normal WHO consultative procedures.

The IMPACT web site would be revised and updated. It would include the proposal for the *Draft principles and elements for national legislation against counterfeit medical products*, inviting comments thereon. A Circular Letter would be prepared to draw Member States' attention to this draft document and the new proposal for the definition of counterfeit medical products contained therein.

A direct link to the above-mentioned document was available in the news section of the IMPACT web site (<http://www.who.int/impact/news/BonnMeetingDraftPrinciples.pdf>).

A proposed revision of the *WHO Good Distribution Practices (GDP) for pharmaceutical products* was discussed by this Expert Committee with a view to its adoption. The document could be found on the WHO web site at: <http://www.who.int/medicines/services/expertcommittees/pharmprep/43rdpharmprep/en/index.html>, and also with a direct link: <http://www.who.int/medicines/>

The planned IMPACT meetings (subject to resources) were as follows:

- regional meeting in South Africa (9–10 November 2009);
- annual meeting of IMPACT Planning Group including all IMPACT Chairs and Co-Chairs (January 2010);
- Open Forum for WHO Member States and interested parties, involving IMPACT partners (January 2010);
- Working Group meetings (January 2010); and
- annual IMPACT meeting (after the World Health Assembly in May 2010).

The Committee was pleased to note the continued cooperation with other WHO departments and programmes.

3. **Quality control — specifications and tests**

3.1 **The International Pharmacopoeia**

Following the publication of the First Supplement to the Fourth Edition, the Expert Committee was informed that the final texts for the monographs adopted at the forty-second and forty-third meetings in October 2007 and 2008 had been made available to users of the WHO Medicines web site and that they were ready to be included in the forthcoming issue of *The International Pharmacopoeia* (Ph.Int.). While the format of this future publication was still to be defined (electronic, CD-ROM or book), a tentative table of contents of about 45 texts for inclusion in this publication was discussed and adopted.

Provisional list of contents for the forthcoming publication of *The International Pharmacopoeia* Monographs adopted at the forty-second meeting of the Expert Committee in October 2007

Pharmaceutical substances

- Lumefantrine
- Zinc sulfate

Dosage forms

- Artemether and lumefantrine tablets
- Magnesium sulfate injection
- Rifampicin and isoniazid dispersible tablets
- Rifampicin, isoniazid and ethambutol tablets

- Rifampicin, isoniazid and pyrazinamide dispersible tablets
- Zinc sulfate oral solution (paediatric)
- Zinc sulfate tablets (paediatric)

Monographs adopted at the forty-third meeting of the Expert Committee in October 2008

Pharmaceutical substances

- Emtricitabine
- Mebendazole (revision of published monograph)
- Nevirapine (revision of published monograph)
- Oseltamivir phosphate

Dosage forms

- Artemether and lumefantrine oral suspension
- Mebendazole chewable tablets (revision of published monograph for mebendazole tablets)
- Chloroquine sulfate oral solution
- Cycloserine capsules
- Efavirenz capsules
- Efavirenz oral solution
- Ethambutol hydrochloride tablets (revision of published monograph)
- Nevirapine oral suspension
- Nevirapine tablets
- Quinine sulfate tablets
- Zidovudine, lamivudine and nevirapine tablets

Radiopharmaceuticals

General monograph and related texts

- General monograph
- Methods of analysis
- Supplementary information
- Individual monographs
- Fludeoxyglucose (^{18}F) injection
- Gallium citrate (^{67}Ga) injection
- Iobenguane (^{123}I) injection
- Iobenguane (^{131}I) injection
- Samarium ethylene diamine tetramethylene phosphonate complex (^{153}Sm) injection
- Sodium iodide (^{131}I) capsules
- Sodium iodide (^{131}I) injection
- Sodium iodide (^{131}I) solution
- Sodium iothalamate (^{125}I) injection

- Sodium pertechnetate (^{99m}Tc) injection (fission)
- Sodium pertechnetate (^{99m}Tc) injection (non-fission)
- Sodium phosphate (^{32}P) injection
- Strontium chloride (^{89}Sr) injection
- Technetium (^{99m}Tc) bicisate complex injection
- Technetium (^{99m}Tc) exametazime complex injection.
- Technetium (^{99m}Tc) mebrofenin complex injection
- Technetium (^{99m}Tc) mertiatide injection
- Technetium (^{99m}Tc) pentetate complex injection
- Technetium (^{99m}Tc) succimer complex injection
- Technetium (^{99m}Tc) sulfur colloid injection
- Technetium (^{99m}Tc) tetrofosmin complex injection
- Technetium (^{99m}Tc) tin colloidal injection
- Technetium(^{99m}Tc) pyrophosphate tin complex injection
- Technetium(^{99m}Tc) methylene diphosphonate (MDP) complex injection
- Technetium(^{99m}Tc) sestamibi complex injection
- Thallous chloride (^{201}Tl) injection
- Yttrium silicate (^{90}Y) colloid injection

The Expert Committee recommended that the texts adopted at the forty-fourth meeting also be considered for inclusion.

WHO Medicines web site — *International Pharmacopoeia* pages

The Expert Committee was pleased to note that regular updates had been made in 2009 of the web pages devoted to the Ph.Int. on the WHO Medicines web site to inform users in a timely manner about recently adopted texts and, when relevant, about specific aspects of the work carried out to develop or revise monographs (e.g. the rapid revision posted for heparins or the note on artemisinin derivatives revision).

In view of the particularity of some of the substances for which monographs had been recently adopted and the large number of new substances included in the 2009 work plan belonging to the same category of medicines, the number of web pages had been increased to include:

- radiopharmaceuticals; and
- anti-infectives (including antibacterial, antiprotozoal, antifungal, antiviral and antimycobacterial agents — for diseases other than HIV/AIDS, tuberculosis and malaria — and anthelmintics).

The Expert Committee noted with appreciation that there had been a positive response to these updates and that requests had been received regarding subscription to a mailing list for receiving alerts on the latest Ph.Int. activities. Recognizing that this mailing system would help users keep track of the latest changes and that this would also improve the dissemination

of information, the Expert Committee recommended the setting up of an automatic notification system of updates or news on the Ph.Int.

One-day briefing on *The International Pharmacopoeia*

The Secretariat informed the Expert Committee that a one-day overview of the Ph.Int. was given in April 2009 to industrial stakeholders. This included describing the process for developing monographs, together with explanations of the pharmacopoeial approach and policy on a variety of issues and of the role of the pharmacopoeia within WHO quality assurance activities. The meeting was interactive and informal to allow manufacturers (mostly those already collaborating with QSM) to raise issues and to have open discussions on the Ph.Int.

It was attended by representatives from generic and research-based pharmaceutical companies as well as pharmaceutical industry associations. The positive feedback received showed that the information provided was helpful and that the briefing session would assist in future collaborations in the development of monographs for the Ph.Int.

In response to requests from the participants to consider a future briefing with a larger audience, the Expert Committee recommended that the WHO Secretariat continue with organizing such information sessions.

3.2 Current work plan and future work programme

In order to respond to the needs of WHO programmes and partner organizations, the Expert Committee agreed in 2008 to only consider for inclusion in the work programme those substances that had been assigned a high priority. A work plan, including a first group of six active pharmaceutical ingredients (APIs) and 36 dosage forms for monograph initiation, was thus adopted.

Since good progress had been made in developing specifications from the 2009 work plan, a new work programme, including a second group for monograph initiation, was proposed to the Expert Committee, taking into account:

- substances remaining from the 2009 work plan;
- substances initially listed in the adopted work programme in 2008 that had now been prioritized, focusing on medicines for children, medicines important for the treatment of HIV/AIDS, tuberculosis and malaria and treatment of diseases with a high prevalence in developing countries);
- additions from the sixteenth Model list of essential medicines and the second List of essential medicines for children;
- additions from the expressions of interests (EOIs) within the WHO Prequalification Programme (PQP); and

— requests for priority medicines recommended in WHO specific disease programmes.

After discussion, the Expert Committee adopted the following new work programme.

Additions to the 2009 work plan are indicated below in bold.

Updated new work programme Medicines used in the treatment of HIV/AIDS and related conditions

API

- **Atazanavir**

Dosage forms

- **Atazanavir capsules**
- Didanosine capsules
- Efavirenz tablets
- **Emtricitabine capsules**
- **Emtricitabine oral solution**
- Ritonavir capsules
- Ritonavir oral solution
- Stavudine powder for oral solution
- Zidovudine tablets

Fixed-dose combinations

- Lopinavir and ritonavir capsules
- Lopinavir and ritonavir oral solution

Dosage forms, including those for paediatric use, as available for:

- **Efavirenz + emtricitabine + tenofovir**
- Lamivudine + stavudine
- Lamivudine + stavudine + efavirenz
- Lamivudine + stavudine + nevirapine
- Lamivudine + zidovudine + efavirenz
- Tenofovir + emtricitabine

Medicines used in malaria treatment

API

- **Piperaquine phosphate**

Dosage forms

- Mefloquine tablets (*used in co-blisters*)

Fixed-dose combinations

- Artemether and lumefantrine capsules
- Artemether and lumefantrine dispersible tablets
- Artesunate and amodiaquine tablets
- Artesunate, sulfadoxine and pyrimethamine tablets
- Sulfadoxine and pyrimethamine tablets (*used in co-blisters*)

Dosage form, including that for paediatric use, as available for:

- Dihydroartemisinin + piperaquine phosphate

Revision

- Artemisinin derivatives (APIs and dosage forms) (see http://www.who.int/medicines/publications/pharmacopoeia/mon_mal/en/index.html)

Medicines used in tuberculosis treatment

APIs

- *p*-Aminosalicylic acid
- Capreomycin
- Levofloxacin
- Ofloxacin
- Terizidone

Dosage forms

- *p*-Aminosalicylic acid granules
- Capreomycin powder for injection
- Ethionamide tablets
- Levofloxacin tablets
- Ofloxacin tablets
- Protionamide tablets
- **Terizidone tablets**

Anti-infectives (antibacterials, antiprotozoal, antifungal, antiviral and antimycobacterial agents, anthelmintics)

APIs

- Ceftriaxone sodium
- Fluconazole
- Ivermectin

Dosage forms

- Albendazole chewable tablets
- Amoxicillin oral suspension
- Ceftriaxone injection
- Doxycycline dispersible tablets

- Fluconazole capsules
- Fluconazole injection
- Fluconazole oral solution/suspension
- Ivermectin tablets
- Levamisole tablets
- Metronidazole oral suspension
- Pyrantel chewable tablets
- Pyrantel oral solution/suspension
- Pyrimethamine tablets

Fixed-dose combinations

- Sulfamethoxazole and trimethoprim injection
- Sulfamethoxazole and trimethoprim oral solution/suspension
- Sulfamethoxazole and trimethoprim tablets

Oral rehydration therapy

APIs

- Zinc acetate
- Zinc gluconate

Dosage forms

- Paediatric zinc acetate oral solution
- Paediatric zinc acetate tablets
- Paediatric zinc gluconate oral solution
- Paediatric zinc gluconate tablets

Various other medicines (analgesics, antipyretics, palliative care, anti-epileptics, large volume parenterals, reproductive health)

Dosage forms

- Carbamazepine oral liquid
- Chewable carbamazepine tablets
- Chewable phenytoin tablets
- Crushable valproic acid tablets
- **Ethinylestradiol + levonorgestrel tablets**
- Glucose intravenous infusion
- **Levonorgestrel tablets**
- **Medroxyprogesterone acetate (DMPA), depot injection**
- Morphine oral solution
- Oseltamivir capsules
- Paediatric retinol capsules
- Paediatric retinol oral solution
- Paracetamol oral solution

- Paracetamol oral suspension
- Phenobarbital oral liquid
- Phenytoin oral liquid
- Sodium chloride and glucose intravenous infusion
- Sodium chloride intravenous infusion
- Valproic acid oral liquid

This updated new work programme would be made available on the WHO Medicines web site.

3.3 **Specifications for medicines, including children's medicines**

3.3.1 ***Medicines for HIV and related conditions***

New monographs for the following antiretroviral active substances and dosage forms were presented to the Expert Committee for discussion. The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the consultative process and those made during discussion.

APIs

- Lopinavir
- Tenofovir disoproxil fumarate

Dosage forms

- Indinavir capsules
- Saquinavir tablets
- Tenofovir tablets
- Lopinavir and ritonavir tablets

A revision of the published text of the following antiretroviral active substance was presented to the Expert Committee for discussion. The revised monograph was adopted, subject to confirmation of the proposed values for the specific absorbance by the collaborating laboratory:

- Efavirenz

3.3.2 ***Antimalarial medicines***

New monographs for the following antimalarial dosage forms were presented to the Expert Committee for discussion. The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the public inquiry and those made during the discussion:

- Amodiaquine tablets
- Quinine bisulfate tablets

Consequent to the development of a new monograph for Quinine bisulfate tablets, a revision of the published text for the quinine sulfate dosage form adopted in October 2008 was required to add an additional identity test allowing the differentiation between the two sulfate forms of quinine possibly used in tablet formulations.

A revision of the published text of the following antimalarial dosage form was thus presented to the Expert Committee for discussion. The revised monograph was adopted, subject to inclusion of the comments received during the public inquiry and those made during the discussion:

- Quinine sulfate tablets

3.3.3 ***Antituberculosis medicines***

Revisions of the published texts of the following antibiotics' active substances, for which an International Chemical Reference Substance (ICRS) was no longer available and thus a new method for assay was needed, were presented for discussion (see paragraph 3.4.2 for antibiotics), together with a new monograph for the corresponding dosage form. The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the public inquiry and those made during discussion:

APIs

- Amikacin
- Amikacin sulfate

Dosage form

- Amikacin injection

New monographs for the following antibiotics active substances and dosage form for which an ICRS was still available, and thus included an assay by a microbiological method, were also presented for discussion. The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the public inquiry and those made during discussion:

APIs

- Kanamycin monosulfate
- Kanamycin acid sulfate

Dosage form

- Kanamycin injection

For the Kanamycin injection monograph, the issue of the determination of the conversion factor from international units (IU) to micrograms was raised. The Expert Committee recommended that this monograph be circulated again for comment on this specific aspect.

3.3.4 *Other medicines*

Oxytocin

A draft proposal for oxytocin was initially sent out for comment in 2007 and presented for discussion at the forty-second meeting of the Expert Committee in October 2008. A revised draft monograph, reflecting the comments received and the Expert Committee's recommendations, was recirculated for comment in January 2009. The new comments received were discussed during the consultation on specifications for medicines and quality control laboratory issues in June 2009, paying special attention to the following aspect of the monograph:

- limits for assay

A revised text was presented to the Expert Committee for discussion. The monograph was adopted, subject to inclusion of the agreed changes, based on the comments received during the public inquiry and those made during the discussion.

Oxytocin injection

A draft proposal for Oxytocin injection was initially sent out for comment in 2007 and presented for discussion at the forty-second meeting of the Expert Committee in 2008. A revised draft monograph, reflecting the comments received and the Expert Committee's recommendations, was recirculated for comment in January 2009. The new comments received were discussed during the consultation on specifications for medicines and quality control laboratory issues in June 2009, paying special attention to the aspects of the monograph presented below.

Storage/stability/pH

The storage of Oxytocin injection was a matter of concern since this injection was widely used in developing countries with hot climates and where refrigeration was not available. It was used by a range of health professionals and health providers (e.g. midwives) as well as in emergency situations. WHO was actively promoting its use by "skilled attendants" for the prevention and treatment of postpartum haemorrhage as part of "Making Pregnancy Safer" (http://www.who.int/making_pregnancy_safer/en/) (Millennium Development Goals for maternal and child health).

The draft monograph circulated in 2007 recommended a storage temperature of between 2°C and 8°C (i.e. in a refrigerator) in line with the recommendations of the major manufacturers. This aspect of the monograph was reviewed by the Secretariat in light of current debate on stability of Oxytocin formulations.

Bearing in mind the application of the Ph.Int., the revised draft circulated for comment in January 2009 retained 2–8°C as the default temperature recommended under Storage, but qualified it by including “unless otherwise indicated on the label”. This recommendation was supplemented by Additional information concerning short-term storage at higher temperatures in line with statements in summary of product information/patient information leaflets (SPCs/PILs) provided by major manufacturers. A Note from the Secretariat invited comment on this aspect of the revised draft together with any supporting data. Based on the above and the comments received, the storage temperature of 2–8°C for the injection was confirmed.

pH value

The lower limit in the revised draft was changed taking account of the limits currently given in other pharmacopoeias.

Related substances

Further to discussion in June 2009, a recently published article demonstrated that the high-performance liquid chromatography (HPLC) method used for the Related substances test currently described in the Ph.Int. monograph for Oxytocin was also suitable to detect the related substances for the injection. The Expert Committee thus recommended using this test in the Oxytocin injection monograph. The details of this method would be added to the revised draft.

The text was presented to the Expert Committee for discussion. The monograph was adopted, subject to inclusion of the agreed changes, based on the comments received during the public inquiry and those made during discussion.

3.4 Revision of texts of *The International Pharmacopoeia*

3.4.1 *Antimalarials: artemisinin derivatives*

The revision of some aspects of the monographs for artemisinin derivatives (Artemether, Artemisinin, Artemotil, Artenimol and Artesunate and their associated dosage forms) was discussed by the Expert Committee in October 2008.

In view of the importance of this category of antimalarial medicines and the time that this extensive revision work would require, an explanatory note including preliminary variations to be carried out to improve the HPLC assay methods (sample preparation) had been posted on the WHO Medicines web site.

Following presentation of a detailed update the Committee was pleased to note that considerable progress had been made; specific revision proposals for two monographs had now been circulated for comment and laboratory work was in progress for other monographs.

The following revised antimalarial dosage forms monographs were presented to the Expert Committee for discussion with the comments received to date. The monographs were adopted, subject to inclusion of the agreed changes, based on the comments made during the discussion and provided no major comments were received during the public inquiry:

- Artesunate
- Artesunate tablets

3.4.2 **Antibiotics**

A number of revision issues related to antibiotics assay were identified and discussed by the Expert Committee at its meetings in October 2006 and 2008.

The Committee was pleased to note that a review had started of those monographs for antibiotics which specified a microbiological assay, with the aim of replacing this method by a chromatographic method where possible. Priority for revision had been awarded to those monographs in Volume 1 of the Fourth Edition of the Ph.Int. that still specified a microbiological assay while the relevant biological reference material (International Standards for Antibiotics (ISA9)) had been disestablished.

The following revision status for these texts (APIs and dosage forms) was presented:

- Amikacin and Amikacin sulfate monographs: the microbiological assay was replaced by an HPLC method using ultraviolet (UV) detection and an alternative method by non-aqueous titration had been added whenever possible. These texts were adopted by the Expert Committee (see paragraph 3.3.3 for antituberculosis drugs);
- Chlortetracycline hydrochloride, Oxytetracycline dehydrate, Oxytetracycline hydrochloride, Tetracycline, Tetracycline hydrochloride and Paromomycin monographs: the Committee agreed to revise these texts taking account of established pharmacopoeial HPLC methods which were also under active revision in other pharmacopoeias. It was, therefore, recommended to await the outcome of these efforts for further discussions of these monographs within the context of the Ph.Int.

As all these revisions were ongoing, the Expert Committee recommended that an information note on the revision status of these monographs be posted on the WHO Medicines web site.

3.4.3 **Other medicines**

Mebendazole

The Expert Committee adopted a modification to the text for mebendazole to improve the interpretation of the revised monograph adopted in October 2008.

Following adoption of the revised monographs for Mebendazole and Mebendazole chewable tablets by the Expert Committee in October 2008, the Secretariat had written to other pharmacopoeial authorities regarding the revision that had been carried out to explicitly restrict the substance to polymorph C in the Ph.Int. In view of the use of mebendazole in intestinal worm eradication programmes worldwide, harmonization of pharmacopoeial monographs had been suggested with respect to the control of polymorphism. The Committee appreciated the helpful replies received from several pharmacopoeias and noted that both the Chinese and European Pharmacopoeias also restricted mebendazole to polymorph C. The possibility of including an explicit statement to this effect within the European Pharmacopoeia (Ph. Eur) monograph was welcomed. It was noted that correspondence from the United States Pharmacopeia (USP) had indicated an interest in harmonizing the USP monograph (which currently did not control the polymorphic form). Members noted, however, that this would not currently be possible since the product currently licensed in the USA contained polymorph B.

The Secretariat undertook to provide feedback to the relevant pharmacopoeial authorities.

Oseltamivir phosphate

The monograph for Oseltamivir phosphate was adopted by the Expert Committee in October 2008 for addition to the Fourth Edition of *The International Pharmacopoeia*.

A further revision for this text was proposed following receipt of comments from manufacturers on the tests for Sulfated ash and related substances. The changes proposed would harmonize the Ph.Int. text with the specifications for oseltamivir phosphate that were now available in other pharmacopoeias (Ph.Eur and USP).

A revised text that included these proposed changes was presented to the Expert Committee for discussion. The monograph was adopted, subject to inclusion of the agreed changes, based on the comments received and those made during the discussion.

3.4.4 **Heparin**

Rapid revisions of the monographs in *The International Pharmacopoeia* for Heparin calcium and Heparin sodium were adopted by the Expert

Committee in October 2008 and had been published on the WHO Medicines web site, to bring them into line with the action of other pharmacopoeias concerning Heparin monographs. The statement on the web site indicated that the WHO Expert Committee on Specifications for Pharmaceutical Preparations, together with the WHO Expert Committee on Biological Standardization, would jointly review the scientific work being carried out by interested parties. The need for further revision of the monographs would be examined, and it was noted that discussion on heparin would be held during the next session of the Expert Committee on Biological Standardization.

Revision of the Heparin monographs was also discussed during the informal consultation in June 2009, when it was recommended to investigate the possible inclusion of a cellulose acetate plate electrophoresis method for the analysis of heparin and its potential glycosaminoglycan impurities, e.g. dermatan sulfate, chondroitin sulfate and oversulfated chondroitin sulfate.

This method, routinely used in industry, had been shown to have a high selectivity for heparinoid impurities and could be performed with low-cost instrumentation. Therefore, this method could be beneficial for small quality control laboratories not equipped for the compendial HPLC methods.

The Expert Committee endorsed the recommendation that the Secretariat, in collaboration with a WHO collaborating laboratory, review the suitability of this proposed method for inclusion in the Ph.Int. and circulate revised draft proposals of the Heparin monographs for comment.

3.5 Review of published general monographs for dosage forms

At its meeting in 2007, the Expert Committee agreed that the general monographs published in Volume 2 of *The International Pharmacopoeia* should be reviewed and revised as necessary, to follow a general monograph “template” that had been prepared, based on the texts adopted for inclusion in the first supplement.

Following the defined template, a draft revision of the general monograph for Tablets was discussed at the informal consultation in June 2009. It was then recommended that, based on the revision of the general monograph for Tablets, a similar revision should be done of the monograph for Capsules. Revised texts for the following monographs were presented to the Expert Committee for discussion. The revised monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the public inquiry and those made during the discussion:

- Tablets
- Capsules

3.6 General policy topics and general revision issues

Several documents including guidance and explanation of the current pharmacopoeial approach as well as a review of application to published monographs for the following general revision issues were presented to the Expert Committee for consideration:

- monographs title and strengths
- strengths available statement
- identity tests
- polymorphism

The Committee discussed the background documents, endorsed the explanatory texts as summarized below and adopted the proposed revisions of the relevant monographs. It further agreed that, as a basis for a future policy, these guidance documents and explanatory texts would be helpful to assist those involved in the development of new and revised monographs. In this respect, the guidance documents might also be made available more widely to provide explanatory information to users of the Ph.Int. by inclusion in the Supplementary information section of the Pharmacopoeia and on the WHO Medicines web site.

Monographs title and strengths

Titles

It was noted that for older monographs the full name of the API was normally included for the dosage form (e.g. Atropine sulfate tablets). In more recent monographs (new texts or revisions) the name of the salt was, whenever possible, usually omitted. There were, however, inconsistencies, e.g. Nelfinavir mesilate tablets.

Following the recommendation of the informal consultation in June 2009, the Expert Committee agreed that a standardized approach should be followed within *The International Pharmacopoeia*, which was to use the shortest title consistent with providing unambiguous information on the nature of the API. Such an approach was designed to facilitate the use of the monograph title for nonproprietary labelling and generic prescribing.

The titles of the following draft monographs presented to the Expert Committee illustrated this approach:

- Indinavir capsules (API — indinavir sulfate)
- Saquinavir tablets (API — saquinavir mesilate)
- Tenofovir tablets (API — tenofovir disoproxil fumarate)
- Amikacin injection (API — amikacin sulfate)

The Expert Committee endorsed the proposal that any change to the title agreed for published monographs could be made either when a monograph

was revised for technical reasons or on publication of a new edition. At such a time, where necessary, the heading Definition would be added together with a statement clarifying the nature of the API used in preparing the dosage form and the Labelling statement would be checked for consistency.

Strengths

How the strength was stated in monographs, and hence the terms in which the content was calculated, was dictated by how products available on the market were labelled. The Committee agreed that having established how the content was declared on the label by the manufacturer and having included in monographs an appropriate labelling statement, where necessary, the content statement under Definition, the calculation under Assay and the amounts of the preparation taken for testing should all be expressed in the same way.

It was noted, however, that problems could arise when product labelling was not clear or where there were inconsistencies between products available on the market. Although it was recognized that neither pharmacopoeial authorities nor WHO had control over product labelling and that this would fall within the responsibility of MRAs, the Committee was informed that a document gathering proposals concerning dosage form terminology and expression of medicine strength was presented by QSM to the Expert Committee for the Selection and Use of Essential Medicines for discussion at its meeting in March 2009.

The Expert Committee welcomed this initiative and was pleased to note that the Expert Committee for the Selection and Use of Essential Medicines broadly endorsed the QSM proposals. As a consequence, the expanded explanatory notes included in the sixteenth WHO Model List of Essential Medicines and in the second WHO Model List of Essential Medicines for Children now included:

- a link to the Quality assurance area of the WHO Medicines web site and to the online text of the current edition of the Ph.Int.; and
- an annex on dosage form terminology.

The Expert Committee for the Selection and Use of Essential Medicines agreed the principles that would be applied to the expression of medicines strengths in future lists and had requested its Secretariat to review current entries and revise them accordingly. These principles were set out in the corresponding Report of the Expert Committee for the Selection and Use of Essential Medicines. WHO Technical Report Series, No. 958, 2010 (in print) as follows.

When revised in accordance with these principles, entries where the active pharmaceutical substance is not the active moiety will more clearly distinguish between:

- those for which the strength is expressed in terms of active moiety (the salt will be indicated in parentheses, e.g. “50 mg (as sodium salt)”); and
- those for which the strength is expressed in terms of API (the salt will be given in full, e.g. “50 mg codeine phosphate”).

Where necessary, in instances of potential confusion (e.g. amodiaquine, quinine salts) a warning note will be included.

Strengths available statement

Monographs in the Ph.Int. for individual dosage forms have included information concerning the strengths of preparations available, referring to “the current WHO Model List of Essential Medicines”. For example, the monograph for Lamivudine tablets published in the first supplement stated:

Additional information. Strengths in the current WHO Model List of Essential Medicines: 150 mg, 300 mg. Strength in the current WHO Model list of essential medicines for children: 150 mg.

This statement was based on information from the fifteenth Model List of Essential Medicines published in 2007. It was, however, noted in 2009 that for lamivudine the then current Model List included only the 150 mg tablets. This example, therefore, illustrated the problem of keeping the strengths available as indicated in Ph.Int. monographs in step with the current Model List of Essential Medicines.

To keep track of changes affecting Ph.Int. monographs each time a new Model List was published would require the user to check for changes frequently, and the Secretariat to continuously revise monographs to correct this non-mandatory information.

The Expert Committee, therefore, endorsed the recommendation that, for the next edition of *The International Pharmacopoeia*, individual monographs would simply include the strengths without the words “in the current WHO Model List of Essential Medicines”. It was agreed instead that the General notices would state that, in general, the strengths indicated under Additional information in individual monographs for dosage forms were those given in the Model Lists. In addition a recommendation could be included to consult the current edition of the Model List and provide a reference to the appropriate page of the WHO Medicines web site (as a link in the electronic version). This would also strengthen the links between the Ph.Int. and the WHO Model List of Essential Medicines (<http://www.who.int/medicines/publications/essentialmedicines/en/index.html>).

Using terms such as “in general” or “wherever appropriate” in the General notices would accommodate the small number of exceptions where a

preparation that was the subject of a monograph was not included in the current Model Lists. Such exceptions included:

- certain preparations recommended by WHO treatment programmes and/or included in WHO treatment guidelines that were not in the Model Lists (e.g. paediatric didanosine oral liquid);
- strengths additional to those in the Model List that had been indicated for similar reasons (e.g. 20 mg Zn strength for zinc sulfate tablets); and
- monographs for products which had been or which might be removed from the Model Lists (e.g. stavudine capsules).

It was also emphasized that, unless restricted by the Definition to a particular strength, a monograph was intended to cover any strength. In this context it was noted that in certain tests (for example, dissolution) explicit reference to particular strengths might sometimes be necessary.

Identity test

Editorial guidance on selection, order and possibility for subsidiary choice of identity tests was discussed.

The current approach, which is to use a combination of different methods within the monograph rather than placing reliance on a single method, was reemphasized. This was particularly important since the Ph.Int. monographs might be applied to material from different manufacturers and by quality control laboratories equipped with different instruments.

Polymorphism

For an API known to exist in more than one morphic form, the way to frame the monograph would depend on whether or not it was restricted to a particular polymorph.

In most cases it was intended that the monograph place no restriction on morphic form. A statement had been included under Additional information to the effect that the substance “may exhibit polymorphism”. In such cases, where an infrared identity test had been included, appropriate instructions were given on how to proceed (see, e.g. the monograph for Efavirenz). Without such instructions the monograph was, in effect, restricting the substance to the morphic form of the ICRS.

3.7 Radiopharmaceuticals

Work on the elaboration of specifications for radiopharmaceuticals was initiated in 2001, with the collaboration of WHO and the International Atomic Energy Agency (IAEA). Following consultations and discussion involving experts from both organizations, agreement was reached that this work would include inter alia the revision of the general monograph in *The International Pharmacopoeia*

and the elaboration of 30 monographs for individual radiopharmaceuticals preparations, to which IAEA had awarded priority in 2005.

Background information on the development of these monographs was presented to the Expert Committee in October 2008 and was described in the forty-third report.

As a result of this joint work, the final versions of the following texts adopted in October 2008 were made available on *The International Pharmacopoeia–Radiopharmaceuticals page* of the WHO Medicines web site.

General monograph and related texts

- General monograph
- Methods of analysis
- Supplementary information

Individual monographs

- Fludeoxyglucose (^{18}F) injection
- Gallium citrate (^{67}Ga) injection
- Iobenguane (^{123}I) injection
- Sodium iodide (^{131}I) injection
- Sodium iodide (^{131}I) solution
- Sodium Pertechnetate ($^{99\text{m}}\text{Tc}$) injection (fission)
- Sodium pertechnetate ($^{99\text{m}}\text{Tc}$) injection (non-fission)
- Technetium ($^{99\text{m}}\text{Tc}$) pentetate complex injection
- Thallous chloride (^{201}Tl) injection

Considering the extensive work already carried out and the need for specifications in *The International Pharmacopoeia* for these pharmaceutical preparations, the 20 remaining monographs (see the list below) were also adopted subject to final scrutiny of the reformatted texts by a small working group composed of experts from both the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and IAEA.

To undertake the editorial work needed to bring the remaining texts in line with those already published on the web site, the Secretariat had agreed with IAEA that the scrutiny would be carried out by the working group by correspondence, following a defined procedure.

Draft monographs for the following substances were sent to the working group in two series of about 10 texts for review:

- Iobenguane (^{131}I) injection
- Samarium ethylene diamine tetramethylene phosphonate complex (^{153}Sm) injection
- Sodium iodide (^{131}I) capsules
- Sodium iothalamate (^{125}I) injection

- Sodium phosphate (^{32}P) injection
- Strontium chloride (^{89}Sr) injection
- Technetium ($^{99\text{m}}\text{Tc}$) bismuthate complex injection
- Technetium ($^{99\text{m}}\text{Tc}$) exametazime complex injection
- *Technetium ($^{99\text{m}}\text{Tc}$) mebrofenin complex injection*
- Technetium ($^{99\text{m}}\text{Tc}$) mertiatide injection
- Technetium ($^{99\text{m}}\text{Tc}$) succimer complex injection
- Technetium ($^{99\text{m}}\text{Tc}$) sulfur colloid injection
- Technetium ($^{99\text{m}}\text{Tc}$) tetrofosmin complex injection
- Technetium ($^{99\text{m}}\text{Tc}$) tin colloidal injection
- Technetium($^{99\text{m}}\text{Tc}$) pyrophosphate tin complex injection
- Technetium($^{99\text{m}}\text{Tc}$) methylene diphosphonate (MDP) complex injection
- Technetium($^{99\text{m}}\text{Tc}$) sestamibi complex injection
- Yttrium silicate (^{90}Y) colloid injection
- Technetium ($^{99\text{m}}\text{Tc}$) labelled Macrosalb ($^{99\text{m}}\text{Tc}$ MAA) injection*
- Technetium ($^{99\text{m}}\text{Tc}$) nanocolloid injection*

* Regarding the monographs for technetium ($^{99\text{m}}\text{Tc}$) nanocolloid injection and technetium ($^{99\text{m}}\text{Tc}$) labelled macrosalb ($^{99\text{m}}\text{Tc}$ MAA) injection, the Committee referred to its decision taken in October 2008 for technetium ($^{99\text{m}}\text{Tc}$) labelled red blood cells injection, when it had been decided that the quality specifications for this type of blood product or derivative, not covered by the Ph.Int., would normally be the responsibility of the WHO Expert Committee on Biological Standardization or would be dealt with through the Blood Regulators Network for which WHO provided the Secretariat. Therefore, it was recommended that the quality specifications for these three biological products derived from albumin be dealt with by the above-mentioned committees.

The comments received thereon were discussed at the informal consultation on specifications for medicines and quality control laboratory issues in June 2009. Revised texts, reflecting the comments confirmed by IAEA, were presented to the Expert Committee for information.

While formatting and reviewing these remaining texts, it was decided that, for the purposes of consistency, some changes needed to be made to all the individual monographs, including to the texts already published on the web site. Revised drafts for those texts were also presented to the Expert Committee for information.

The Expert Committee noted with appreciation the completion of this work and endorsed the reformatted monographs prepared following the recommendations made in 2008. It further agreed that those final texts be placed on *The International Pharmacopoeia–Radiopharmaceuticals* page of the WHO Medicines web site, bringing the number of new individual monographs for radiopharmaceutical preparations for inclusion in the Fourth Edition of *The International Pharmacopoeia* to 27.

4. Quality control — international reference materials (International Chemical Reference Substances and International Infrared Reference Spectra)

4.1 Annual report of the WHO Collaborating Centre

The Expert Committee noted with appreciation the work carried out by the WHO Collaborating Centre for Chemical Reference Substances as presented in its report for 2008. It was noted that the total number of International Chemical Reference Substances (ICRS) distributed from the Centre in 2008 was 2153 compared to the 2332 reported in 2007. The most frequently requested substances included artesunate, artemether, prednisolone, artemisinin and zidovudine impurity B.

The Expert Committee adopted the report for 2008.

4.2 Adoption of new International Chemical Reference Substances

Nine ICRS were established in 2008, including the following seven new substances:

- carbidopa
- colchicine
- lumefantrine
- DL-methionine
- naloxone hydrochloride
- oseltamivir for system suitability
- oseltamivir phosphate

and the following replacements:

- artemisinin
- prednisone

The Expert Committee adopted the above-listed ICRS.

4.3 New institution for the establishment of international reference materials

While adopting its activities report for 2008, the Expert Committee was also informed that, since May 2009, Apoteket AB in Sweden had ceased its activities as host of the WHO Collaborating Centre for Chemical Reference Substances and that these activities were in the process of being transferred to a new institution.

It was emphasized with appreciation that Apoteket AB had started its collaboration with WHO and specifically *The International Pharmacopoeia* in 1956. In recognition of Apoteket AB's longstanding services to WHO, the Expert Committee expressed its gratitude to the WHO Collaborating Centre on Chemical Reference Substances and to the Government of Sweden which had supported these activities over the past 53 years.

Recognizing the inconvenience caused by this transition from the former Collaborating Centre to the new institution, notably for the distribution of ICRS, the Expert Committee welcomed the announcements posted on the WHO Medicines web site to inform users during this transitional period. As this process was nearing finalization, another announcement indicating the new contact details for ordering ICRS was soon expected to be published.

As regards the new institution, the Committee made some proposals on the content of the future activity report and encouraged the possibility of reflecting in more detail certain activities such as the stability monitoring of ICRS. The Expert Committee also welcomed the future efforts of the Secretariat in assisting the new institution with regard to collaborative trials to identify any additional laboratories for the establishment of new ICRS. Pricing for the distribution of ICRS was also discussed and the Expert Committee was informed that owing to the change of currency with which the new institution would operate, the price of the ICRS would need to be adjusted. It, therefore, agreed that the price, which had not been changed over the past decade, be increased.

The Committee stated that it would look forward to receiving annual reports on work carried out on ICRS from the new institution.

5. Quality control — national laboratories

5.1 External Quality Assurance Assessment Scheme

The External Quality Assurance Assessment Scheme (EQAAS) aimed to give each laboratory the opportunity to measure its performance through a confidential system of testing of blind samples and to determine its ability to perform a given analytical procedure within a network of governmental control laboratories. The system was aimed at reinforcing mutual confidence within this network.

With a view to continuing the promotion of quality assurance in drug quality control laboratories in WHO Member States, five test series of Phase 4 of a proficiency testing scheme had taken place. Some 50 laboratories had participated in this phase of the Scheme, which was now finalized.

The Committee noted the final reports on the five tests and the preliminary summary report for Phase 4 of this Scheme. The results reported were:

- final report procedure 1: determination of water by the Karl Fischer method
- final report procedure 2: dissolution testing
- final report procedure 3: assay of tablets by HPLC
- final report procedure 4: assay by titration
- final report procedure 5: optical rotation by polarimetry
- summary report, Phase 4

During the informal consultation held in June 2009, the experts considered the Scheme to be most efficient, both for the participating laboratories and for the feedback on the methods from the Ph.Int. used in the Scheme. They strongly recommended continuation of the Scheme starting with a new phase. In addition they advised on how to revise the Ph.Int. methods used, e.g. in procedure 4.

Regarding the samples, the experts from the consultation advised the retention of extra samples from each procedure for those laboratories which gave doubtful or unsatisfactory results and which would need to redo testing. Moreover, WHO should strongly encourage the participating laboratories to report back to WHO on the outcome of such investigations and follow-up actions, as necessary.

The Expert Committee acknowledged with thanks receipt of the samples from UNICEF and from the manufacturers involved.

Further to the previous agreements between WHO and EDQM (dated 21 March 2000, 26 January 2001, 8 July 2004 and 15 March 2007), it was decided to continue collaboration during the period 1 January 2010–31 December 2012 with a view to evaluating the technical performance of 60 drug quality control laboratories designated by WHO for participation in the EQAAS, in accordance with the programme of proficiency testing schemes developed by EDQM, in the following analytical procedures:

- assay by titration (sample: metronidazole)
- water content by Karl Fischer (sample: amodiaquine dihydrochloride dihydrate)
- dissolution test (sample: artemether and lumefantrine tablets)
- related substances by HPLC (sample: abacavir oral solution)
- assay by HPLC (sample: amodiaquine tablets)
- dissolution test (sample: rifampicin capsules)
- related substances by thin-layer chromatography (TLC) (sample: artemether and lumefantrine oral suspension)

The proposed programme could be modified depending on the availability/ expiry dates of the substances (testing samples and reference materials) and/or the availability of the methods.

The Expert Committee endorsed the recommendation of the informal consultation and welcomed the new phase currently in preparation with EDQM.

5.2 WHO good practices for quality control laboratories

Revision of WHO good practices for pharmaceutical quality control laboratories (GPCL)

At its forty-third meeting the Expert Committee recommended that the WHO Secretariat initiate the process of revision of the *WHO good practices for national pharmaceutical control laboratories* (*Good practices for national pharmaceutical control laboratories*, Annex 3, WHO Technical Report Series, No. 902, 2002 (http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf#page=37)).

The following requirements were set for the revision, based on the recommendations of the Expert Committee at its forty-third meeting:

- include the most important parts of the WHO GMP guide, which were relevant to quality control laboratories, directly in the GPCL guideline and add references to other relevant parts of the WHO GMP guide;
- provide detailed guidance for the areas identified as being often deficient during inspections performed by the PQP;
- align the guidance with the requirements of ISO/IEC 17025:2005;
- apply to any pharmaceutical quality control laboratory, be it national, commercial or another nongovernmental laboratory; and
- harmonization of terms used in other WHO documents.

The first draft revision was prepared in March 2009 and was widely commented on. The comments received were discussed with laboratory experts at the informal consultation on specifications for medicines and quality control laboratory issues in June 2009 following which a second draft revision was prepared. The second draft revision was further discussed with inspectors in the informal consultation on WHO guidelines for medicines quality assurance, quality control laboratories and transfer of technology in July 2009, resulting in a third draft revision which was distributed for comments in September 2009.

This third draft revision was presented for discussion to the forty-fourth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

The following changes were made to the original guidelines published in 2002:

— ***Explanatory notes***

In order to differentiate between requirements and advice, explanatory notes were introduced in the text.

— ***Glossary***

Definitions were revised to bring them into line with current WHO documents and 15 definitions were added as a reflection of the extended text. Definitions from WHO guidelines were used where available, or else definitions were adopted from widely accepted documents such as *International Vocabulary of Metrology* published by the Joint Committee for Guides in Metrology.

— ***Part one — Management and infrastructure***

The *Organization and management* and *Quality system* sections were amended and structured in such a way as to provide clearer guidance. Explicit requirements on internal audits, management review of quality issues, corrective and preventive measures were included. The *Control of documentation* section was substantially extended and the *Record* section was amended to provide electronic records. The section on *Personnel* was simplified to provide a laboratory with more flexibility in organization while assuring the essential functions. Requirements on *Premises* were focused more on chemical testing and for the requirements for microbiological testing and testing on animals, readers were referred to other guidelines. The section on *Contracts* was added, differentiating between contracts to purchase services and supplies and subcontracting tests.

— ***Part two — Materials, equipment, instruments and other devices***

Requirements on labelling of reagents, reagent solutions and volumetric solutions were specified in detail. Reference substances and reference materials were differentiated and clarification was provided on retesting of various types of reference substances. Requirements relating to the qualification of laboratory equipment were added, referring to the WHO guidelines. The section on *Traceability* was simplified.

— ***Part three — Working procedures***

The requirement for review of a test request by the laboratory was included. In the case of a pharmaceutical manufacturer's laboratory, the test request form could be replaced by a master production instruction. A section was added dealing with validation of analytical procedures and system suitability test, including the requirement to demonstrate that a pharmacopoeial method or externally validated analytical method was suitable for the substance or product to be tested. Detailed guidance on

the procedure for out-of-specification results, including references to the US Food and Drug Administration (FDA) and the European Official Medicines Control Laboratories (OMCL) network under the *Note* was provided. A brief explanation of uncertainty of measurement with further references was included. The contents of the analytical test report, which was used in investigative testing, and of the certificate of analysis were specified.

— ***Part four — Safety***

No major changes were made to part four.

— ***References***

References to WHO documents were updated and a number of references to documents of other organizations, such as the International Organization for Standardization, Joint Committee for Guides in Metrology, US FDA, International Society for Pharmaceutical Engineering, European Union guidelines, the OMCL Network of the Council of Europe, US Pharmacopeia, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and Eurachem/Cooperation on International Traceability in Analytical Chemistry (CITAC), were included under *Notes*.

— ***Appendices***

Appendix 1: *Model analytical test report for active pharmaceutical ingredients, excipients and pharmaceutical products* was deleted and was replaced by a reference to existing WHO guidelines.

Appendix 2 (now Appendix 1): *Equipment for a first-stage and medium-size pharmaceutical quality control laboratory* did not represent any requirement; it would be helpful in establishing a new laboratory in a developing country. The list, which covered chemical and microbiological units, was updated according to currently used analytical methods and equipment and specific requirements for a pharmacognosy/phytochemistry unit were added.

— ***Applicability to any pharmaceutical quality control laboratory, be it national, commercial or another nongovernmental laboratory***

Due attention was paid to the applicability of the guidelines. The inappropriateness of some requirements in the first draft, specifically to laboratories belonging to a pharmaceutical manufacturer, was commented upon by several organizations. The text was subsequently thoroughly discussed with GMP inspectors during the aforementioned informal consultation and modified accordingly. Recommendations specific to national pharmaceutical quality control laboratories were stressed and some flexibility was introduced.

The revised guidance text was presented to the Expert Committee for discussion of comments and this was adopted (Annex 1).

5.3 WHO good practices for pharmaceutical microbiology laboratories

Introduction

In addition to the above-discussed update of the WHO good practices for pharmaceutical control laboratories, during the inspections carried out when prequalifying laboratories, the inspectors had noticed that these guidelines might benefit from complementation by a specific text for pharmaceutical microbiology laboratories.

In light of the above, the Expert Committee recommended that the WHO Secretariat initiate the process of revision of these good practices and in addition prepare a new text on good practices for pharmaceutical microbiology laboratories. The Committee took note that these guidelines were in production and would be sent out for comments.

6. Quality assurance — good manufacturing practices

6.1 WHO good manufacturing practices: main principles for pharmaceutical products

An informal consultation on WHO guidelines for medicines quality assurance, quality control laboratories and technology transfer was held in Geneva from 27 to 31 July 2009. *WHO GMP: main principles for pharmaceutical products* was discussed with the following outcomes:

The main changes recommended during that meeting and subject to presentation to the Expert Committee for review and possible approval were as follows:

- quality unit concept to be included in the main principles;
- inclusion of the quality risk management;
- addition of a reference and link to the product quality review; and
- more detailed review of the responsibilities of key personnel.

The main changes recommended were:

- Quality unit concept
- Quality risk management
- Product quality review
- Responsibilities of key personnel.

The Expert Committee endorsed the suggested recommendations and recommended that the Secretariat distribute the revised text for comment.

6.2 WHO good manufacturing practices for active pharmaceutical ingredients

During several previous meetings of the Expert Committee, the revision of WHO GMP for active pharmaceutical ingredients (APIs) had been discussed. The Committee also closely followed development of the ICH GMP guidelines for APIs, including their initial preparation by the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

In the past the Committee had recognized the difficulty that countries would have in implementing the ICH GMP guide in a short period of time. It, therefore, agreed that WHO should revise the current WHO GMP for APIs to reflect current GMP requirements and to take into account other published guidelines, including the ICH guide. The Committee endorsed the step-wise approach to the implementation of GMP for APIs.

In the meantime, the principles described in the ICH GMP for APIs had been recognized and implemented by numerous national inspectorates. In addition, they had been field-tested when inspecting in the context of the WHO PQP (for medicines).

The Secretariat had, therefore, prepared a WHO-style, edited version of this guide, fully in line with the internationally used text developed following the ICH process.

This draft working document was reviewed and discussed with inspectors, experts and interested parties during the informal consultation in July 2009. During this meeting it was recommended that the text be fully retained in line with the ICH principles in order to avoid any challenges regarding the further global implementation of this standard internationally.

In order to further assist with its implementation, the experts decided to add clarifying notes and explanations for some of the parts that had been questioned during inspections, i.e.

- definition of API starting material;
- (para. 2.1.1) role of senior management regarding the implementation of an effective quality management system;
- (para. 2.3) delegation of the responsibility for production activities;
- need for manufacturers of intermediates and/or APIs to have a system for evaluating the suppliers of critical materials in place;
- examination of each container or grouping of containers of materials upon receipt and before acceptance;
- identification of batch material;
- reserve samples; and
- inclusion of cross-references to *Good trade and distribution practices* (GTDP) and GMP for excipients in the section entitled: Agents, brokers, traders, distributors, repackers and relabellers.

The Expert Committee endorsed the above recommendations and considered the establishment of a small working group to finalize the wording of the explanatory notes. It agreed to the publication of the supplementary GMP text for APIs together with the explanatory notes to replace the GMP for APIs published in 1992 (Annex 2).

6.3 WHO good manufacturing practices for pharmaceutical products containing hazardous substances

A working document (“WHO guidance to the inspection of hormone product manufacturing facilities”) had been prepared previously and tabled at the Expert Committee meeting held in October 2008. These particular guidelines were intended to provide GMP principles for the production and control of products containing certain hormones or other hazardous substances.

There was international concern about the low quality of reproductive health products and the lack of compliance with GMP principles in manufacturing facilities. The PQP included reproductive health products, and to further facilitate improved quality of manufacture of these products, the Expert Committee acknowledged its previous recommendation to provide guidance in this area.

A discussion with experts and interested parties took place during the consultation held from 27 to 31 July 2009. Considering all recommendations for amendment, the group recommended that the title of the document be changed to address not only products containing certain hormones, but also to ensure that the document and the title reflected the wider group of products containing hazardous substances. A revised version of the working document was, therefore, prepared for circulation and was mailed out for comments.

The new working document QAS/08.256/Rev.1 was submitted to the Expert Committee.

The text was presented to the Expert Committee for discussion of comments and the guidelines were adopted (Annex 3) after a review of all outstanding questions.

6.4 WHO good manufacturing practices for sterile pharmaceutical products

The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted in its thirty-sixth report in 1999, WHO good manufacturing practices for sterile pharmaceutical products (WHO Technical Report Series, No. 902, 2002, Annex 6) (<http://whqlibdoc>.

who.int/trs/WHO_TRS_902.pdf). This guidance was also published in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2. Second updated edition. Good manufacturing practices and inspection* (2007).

Following implementation of these WHO GMP within the context of the PQP, a proposal for revision was being submitted to take into consideration new developments and to bring it into line with International Standardization Organization standard ISO 14644-1 and recent EU, Japanese, PIC/S and US practices.

The following major changes had been made to the text published in 1999:

- New chapters on “Isolator technology” and “Blow/fill/seal technology” had been added.
- The chapter on “Finishing of sterile products” had been amended and provisions had been given for capping of vials.
- The chapter entitled “Manufacture of sterile preparations” had been amended and provisions given for clean-room and clean-air-device monitoring.

Implementation of certain parts of these new practices might need to be undertaken for using a step-wise approach, especially the part relating to the provision for capping in a clean or sterile environment, as this was currently not implemented in most industries.

The text was presented to the Expert Committee for discussion of comments and the guidelines were adopted (Annex 4), after review of the additional comments received by the deadline set for comments to be discussed at the meeting.

6.5 Updates of other WHO good manufacturing practices texts

It was reported that during inspections when implementing the GMP for heating, ventilation and air-conditioning (HVAC) a need for slight revisions to certain chapters was noted. It was, therefore, suggested that these chapters be sent out for comments.

The Expert Committee endorsed this suggestion and recommended that the Secretariat distribute the revised text for comment.

6.6 Good manufacturing practices for blood establishments

An update on the developments of the WHO GMP for blood establishments was presented to the Committee. There was an agreed need for quality and safety requirements, specifications and standards for blood and plasma collection, preparation, testing and distribution activities, the

implementation of internationally agreed quality and safety standards in the blood establishments, a harmonized and systematic approach to ensure compliance at all steps involved (from donor acceptance to release of products), and enforcement by competent MRAs.

ICDRA had recommended the following at its 13th meeting held in Berne in 2008:

“Recognizing the worldwide need for blood products regulation to ensure availability of safe blood and blood products in the face of known and emerging threats, including emerging infectious diseases, WHO should:

- Take steps to further develop and strengthen national/regional blood regulatory authorities and to promote cooperation
- Provide harmonized 'assessment criteria for blood regulatory systems' (BRN): convene a consultation of NMRAs to review Draft assessment tool
- Prioritize development of WHO Guidelines on GMP for Blood Establishments
- Promote introduction of WHO recommended plasma standards by NMRAs.”

WHO had issued requirements for the collection, processing and quality control of blood components and plasma derivatives (WHO Technical Report Series, No. 840, 1994, Annex 2) and recommendations for the production, control and regulation of plasma for fractionation (WHO Technical Report Series, No. 941, Annex 4). In addition, the GMP guide for blood establishments had been published by bodies such as the PIC/S.

Based on the above, the project for WHO guidelines on GMP for blood establishments was intended to respond to the ICDRA recommendation, without inventing a new GMP standard, but taking into account the specifics of blood products, blood establishments and all existing complementary GMP standards.

The aim of the new document was to establish a wide international consensus on quality standards among blood establishments and among inspectors to ensure high-quality products and safety of recipients. It would then become a guidance document for blood establishments, for NMRAs to refer, implement and enforce GMP in blood establishments and to become widely applicable, independent of the activities of a single blood establishment.

The document addressed the general GMP topics, e.g. quality management, as well as the topics specific to manufacturing of blood products, from donor selection through distribution of final products and the newer GMP concepts, e.g. risk management and product quality review.

The detailed structure of the current working document was presented. This included the following chapters: Introduction, Glossary, Quality management, Manufacturing, Contract manufacturing, Analysis and services and a section on Authors, References and History.

The chapter on manufacturing included detailed process-specific guidance, covering donor registration, donor selection, collection, component preparation, laboratory testing, quality control, labelling, release, dispatch, shipping and returns. The product characteristics comprised whole blood, red cells, platelets, plasma for transfusion/fractionation and cryoprecipitate/CPP. The points to consider for validation of preparation steps would focus on centrifugation, separation, freezing, leukocyte reduction and irradiation.

The drafting process had started in January 2008. The text was reviewed during a WHO training workshop (in Teheran) in November 2008 and again in its revised format by a consultation of experts from July to September 2009. The text would also be presented for discussion to the ECBS in October 2009 and released for open consultation. It was expected that subsequent to the global consultation, review of comments and further revision of the document, it would be presented to the ECBS in 2010 with a view to adoption.

The comprehensive consultation process involved WHO Member States through WHO channels (e.g. ministries of health), WHO Regional Advisers, targeted regulatory authorities, blood transfusion services and professional institutions and associations and other interested parties through its publication on the WHO web site.

The Expert Committee took note of the progress made and recommended that this text be mailed out for comment to the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and again be presented at the next meeting of the Committee with a view to its adoption within the full set of GMP texts.

7. Quality assurance — new approaches

7.1 Risk analysis

Introduction

During the meeting of the Expert Committee in October 2007, an update on the new ICH Q10 was given to the Committee by the Secretariat. The Committee concluded that the ICH Q8, Q9 and Q10 documents were useful tools.

On the topic of risk analysis, the Committee made recommendations for WHO to:

- review and update the WHO guidelines on hazard analysis and critical control points (HACCP);
- revise the main text of the WHO GMP to include the principles of application of risk management.

Considering the changes in the approach to quality risk management in the regulatory environment and the use of different tools to analyse risk, the Secretariat had started the process of reviewing the WHO guidelines on HACCP and expected to submit the proposed revised guidelines to the Expert Committee at its next meeting.

Recommendation

The Expert Committee:

- supported the Secretariat in continuing the preparation of the revised draft guideline on HACCP; and
- encouraged the Secretariat to include the principles of quality risk management and to provide examples of possible tools that may be used in quality risk management — not only focusing on HACCP.

7.2 WHO guidelines on technology transfer

The need for new WHO guidance on transfer of technology was discussed at the forty-second meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2007. Colleagues from the WHO PQP shared their experience of recently submitted dossiers by, and inspections carried out in, plants that had undergone technology transfer. Technology transfer was happening worldwide both within and between companies, and within the same country as well as between countries. The Expert Committee, therefore, recommended that WHO guidelines on transfer of technology be developed. A draft document was subsequently prepared and sent out for comment. It was then discussed during the consultation on WHO guidelines for medicines quality assurance, quality control laboratories and transfer of technology on 27–31 July 2009 and a revision was prepared.

The Expert Committee discussed and reviewed the major points that were raised during the commentary period, keeping the balance between GMP and business criteria. Inclusion of the concept of quality by design and the possibility of optional requirements depended on the type of transfer. The Committee took note that the Secretariat would organize a consultation and prepare a new working document for wide circulation following the usual consultation procedure.

8. Quality assurance — distribution and trade of pharmaceuticals

8.1 WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce

The WHO Certification Scheme for finished pharmaceutical products was an international voluntary agreement intended to provide assurance to countries participating in the Scheme, about the quality of pharmaceutical products moving in international commerce (World Health Assembly resolution WHA22.50 (1969), World Health Assembly resolution WHA28.65 (1975), World Health Assembly resolution WHA41.18 (1988), World Health Assembly resolution WHA45.29 (1992), World Health Assembly resolution WHA50.3 (1997)). The primary document of the Scheme was the Certificate of Pharmaceutical Product (CPP).

The Expert Committee had recommended during discussion in 2008 that the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce should be reviewed in light of the changing environment, including the rapid globalization of the pharmaceutical manufacturing sector coupled with changes in the make-up of both the regulators and the groups involved in procurement. In addition, it acknowledged that legislation had been put in place in various countries and regions to assess products manufactured in them and produced for “export only”, for which there was currently no adequate provision in the Scheme.

An oral presentation was given by the Secretariat of the work it had done following the recommendations made at the previous meeting of the Expert Committee.

Questions and answers

Based on the Committee’s recommendations a question and answer paper was prepared in the interim on the function of the Scheme.

The first working document was based on the feedback, draft questions and answers received from the International Federation of Pharmaceutical Manufacturers and Associations/European Federation of Pharmaceutical Industries and Associations (IFPMA/EFPIA). The working document was subsequently circulated for comments.

Reviewing all the comments received and the materials already available, a new set of questions and answers was prepared and made available.

An additional question and answer was provided for further discussion at the Expert Committee, raised by the specialist who had reviewed all

comments received and who had drafted a new set of questions and answers. This question referred to the possibility of a CPP to be used to provide evidence of an administrative review and approval (e.g. as certification of acceptability of a company name change).

The Expert Committee:

- noted the updated report from the Secretariat;
- reviewed the document and considered the additional question; and
- approved the questions and answers for posting on the WHO web site and publication in *WHO Drug Information*, with the possibility to receive comments and to review any question(s) and answers.

8.2 WHO good distribution practices for pharmaceutical products

Following the adoption of the WHO guidelines for good distribution practices (GDP) by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its fortieth meeting in October 2005 (http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=191) (WHO Technical Report Series, No. 937, Annex 5, 2006) these guidelines had been revised by the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) partnership to strengthen the potential for prevention of counterfeit and other illegal medicines entering the supply chain. The following text outlines the process followed.

At an IMPACT meeting held in Bonn, Germany, in November 2006, the existing GDP was reviewed and amendments proposed relating to the specific issue of improving the security of the distribution chain vis-à-vis counterfeits. This was based on the consideration that even in highly regulated countries counterfeit medicines reached patients through the regulated distribution chain.

A first draft was circulated in March 2007 to all the members of IMPACT's Regulatory Implementation Working Group (IRIWG). The IRIWG subsequently met in Washington, DC, USA from 23 to 25 April 2007 and discussed inter alia the draft and recommended amendments. A revised draft was circulated among the members of IRIWG and a final draft was then made available on the WHO web site for further comments. All IMPACT members (including the MRAs of 60 WHO Member States, plus other stakeholders) were actively encouraged to provide comments.

The draft was further revised and then finalized at the General Meeting of IMPACT held in Lisbon, Portugal, in December 2007. This text reflected the consensus reached at the Lisbon meeting and was submitted to the

WHO Expert Committee in 2008 as a recommendation from the IMPACT partners.

During its forty-third meeting the Committee recommended discussing the document further with IMPACT, the EU and with WHO in view of the comments received. A meeting was subsequently arranged in Geneva on 31 August–1 September 2009 with a view to preparing a new document containing all comments received from the various parties and members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations. The revised document resulting from this meeting was presented to the Expert Committee at its current meeting and the main comments received up until the date of the meeting were identified and discussed. A small subgroup was formed to review all comments received by the permissible deadline. The Committee adopted the text subject to input from this subgroup and provided no major additional comments were received. The Committee members would be duly informed of the outcome (Annex 5), in order to allow them to reconfirm their decision in light of the deliberations of this Expert Committee subgroup.

8.3 **Regulatory oversight on pharmaceutical cold chain management**

Following-up on the 2008 joint session of topics with common interest, the Secretary of the Expert Committee for Biological Standardization (ECBS) arranged for an update in relation to the draft *Regulatory oversight on pharmaceutical cold chain management. Harmonized guidance for the storage and transport of temperature-sensitive pharmaceutical products*. The table of contents of the current draft working document was presented to the Committee for information.

The document had been developed with a group of experts and took forward the agreement from the joint meeting between the two Committees in 2008, as one of the cross-cutting issues. The document was considered to be fairly mature and would be presented at the 2009 ECBS meeting to obtain feedback, with a view to possible adoption of the document in 2010.

An oral update by video was given by the technical officer responsible for this project.

The Expert Committee noted this update and suggested circulation of the document to the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and to the IMPACT IRIWG that developed the revision of the GDP.

9. **Prequalification of priority essential medicines**

9.1 **Prequalification Programme managed by WHO**

The WHO Prequalification Programme (PQP) ensured that medicines procured with international funds were assessed and that the manufacturers of these medicines were inspected, in order to provide a high level of assurance of their quality, efficacy and safety. This was supported by building national regulatory capacity, providing technical assistance to selected manufacturers and postmarket monitoring through quality control (QC) testing by prequalified quality control laboratories. Ultimately the aim was to make low-cost quality priority medicines available for the benefit of those in need.

PQP continued to expand in order to meet the needs of procurers and currently covered priority essential medicines in the following areas:

- HIV/AIDS
- tuberculosis
- malaria
- reproductive health
- selected individual products for other diseases such as oseltamivir and zinc sulfate.

Manufacturers were invited to apply for prequalification of medicines included in invitations for Expressions of Interest (EOI) published on the PQP web site.

The Programme was reliant upon and appreciated the assistance and support of many partners, including national medicines regulatory authorities (NMRAs), QC laboratories, WHO disease departments and programmes, regional and country offices, United Nations and other drug procurement agencies (including UNICEF, the Global Fund and Médecins Sans Frontières) and donors such as the Bill and Melinda Gates Foundation and UNITAID, as well as the colleagues of the Medicines Quality Assurance and Regulatory Support Programmes of WHO. The Programme relied heavily on the standards and guidelines adopted by this Expert Committee.

Assessment of product dossiers (see Table 1)

Assessment of product dossiers was conducted both in-house and by external international experts. WHO standards as defined in WHO guidelines and *The International Pharmacopoeia* were applied. If these did not exist, ICH guidelines were used and, in case of need, guidelines of stringent

regulatory authorities were applied. Much of the assessment work was done in Copenhagen during bimonthly meetings of 15–20 assessors. Variations to prequalified products were processed in-house and during the meetings in Copenhagen.

Table 1

Assessment of product dossiers: statistics

	2007	2008	2009 (As at 16/09/2009)
Products prequalified	21	40	24
Dossiers submitted	90	92	55

Medicines assessed and prequalified by WHO were included in a List of WHO Prequalified Medicinal Products on the PQP web site. Also listed were medicines assessed by SRAs, following an abbreviated procedure.

Currently prequalified products (16 September 2009):

- 247 for treatment of HIV/AIDS and related diseases
- one for treatment of influenza (prequalified in 2009)
- 23 for treatment of tuberculosis
- 16 for treatment of malaria
- 2 for reproductive health (prequalified in 2009)
- Total: 289

Inspections of manufacturers (see Table 2)

Manufacturers of finished products, selected APIs and also selected contract research organizations (CROs) (which carried out clinical/bioequivalence studies) were inspected as part of the prequalification process.

Inspections were conducted by a team of inspectors consisting of:

- a WHO lead GMP inspector
- an inspector from a well-established inspectorate
- national inspectors from the country of the manufacturer, who were invited to be part of the team as observers but had no decision-making power (because of different GMP standards and potential conflict of interest)
- inspectors from developing target countries who might also be invited as observers, for capacity-building purposes.

Table 2

Inspections carried out since 2005

Manufacturer:	2005	2006	2007	2008	2009 (to September)
Finished product	20	17	26	27	22
Active pharmaceutical ingredient	10	10	6	11	5
Contract research organization	14	15	13	14	6
Quality control laboratory	3	1	1	6	3

Prequalification of medicines — transparency

The World Health Assembly through Resolution WHA57.14 of 22 May 2004, requested WHO:

“3. (4) to ensure that the prequalification review process and the results of inspection and assessment reports of the listed products, aside from proprietary and confidential information, are made publicly available.”

A WHO Public Assessment Report (WHOPAR) provided a summary of the dossier assessment (where found to be compliant).

A WHO Public Inspection Report (WHOPIR) provided a summary of the inspection (where found to be GMP-complaint).

A Notice of Concern (NOC) was a letter reflecting areas of concern where the non-compliances required urgent attention and corrective action by the manufacturer or research organization.

A Notice of Suspension was a letter reflecting areas of concern when deficiencies identified during an inspection indicate significant non-compliance with GMP, good clinical practices (GCP) or good laboratory practices (GLP), as relevant, resulting in inadequate assurance of product quality.

Prequalification of QC laboratories

The PQP was established in 2004 for QC laboratories in Africa only; however, the programme had since broadened its scope for participation and was now voluntary and without regional limitation. Any laboratory (private or governmental) could participate and the programme was free of charge. The third invitation for EOI was published in September 2007 at the following address: http://www.who.int/prequal/info_applicants/eoi/EOI-QCLabsV3.pdf.

Priority regarding assessment was given to national QC laboratories, laboratories providing testing services to the government, and QC laboratories in areas where United Nations agencies had identified the need for quality testing.

Monitoring after prequalification involved:

- re-inspections at regular intervals
 - normally three years
 - two re-inspections performed;
- a brief report to be submitted annually
 - summary of services provided to United Nations agencies, number of samples analysed, methods used, complaints received
 - brief details of proficiency testing
 - changes to key personnel, facility, equipment or other change with significant impact on the laboratory
 - update of the laboratory information file (LIF), in case of changes with significant impact on LIF content;
- evaluation of results from participation in proficiency testing
 - WHO EQAAS, Agence française de sécurité sanitaire des produits de santé (AFSSAPS) network of francophone African countries;
- WHO might suspend or withdraw a laboratory from the list when there was evidence of noncompliance.

At present the PQP had surpassed expectations and a significant number of laboratories around the world were applying for prequalification.

The object was to increase access to QC laboratories that met recommended standards and that were committed to providing a service to United Nations agencies for testing of medicines, including but not limited to HIV/AIDS, tuberculosis and malaria products.

As of September 2009, there were 11 prequalified laboratories in: Algeria; France; India; Kenya (2); Morocco; Singapore (2); South Africa (2); and Viet Nam.

The PQP was also involved in capacity building: technical assistance provided to eight national medicines QC laboratories; training in quality assurance, quality control and Ph.Int. (2007); a seminar on rational sampling and testing in quality control of medicines (2009); and participation in EDQM in quality assurance training for official medicines control laboratories (2007). The Programme also monitored the quality of medicines through its policy, sampling and testing projects and prequalified laboratories or laboratories for which the evidence of reliability was available. The major quality monitoring projects were the following:

Quality monitoring of medicines funded by UNITAID (2008/9)

The pilot phase focused on paediatric and second-line antiretrovirals and co-trimoxazole-containing medicines. In cooperation with NMRAs in Kenya, Uganda, the United Republic of Tanzania and Zambia, 378 samples produced by 24 manufacturers were collected, mostly from treatment centres and tested in the laboratory. Only three samples did not

comply with specifications and none of the failures were life-threatening for patients. The majority of the products collected were prequalified by WHO. The project served to strengthen quality control of medicines funded by UNITAID and to capacity building of NMRAs involved.

Quality survey of antimalarial medicines in Africa (2008-2009)

A quality survey of antimalarial medicines focused on artemisinin-based combination therapies (ACTs) and sulfadoxine-pyrimethamine oral dosage forms was performed in six African countries; 936 medicine samples were collected at all levels of the distribution chain and the informal market and were screened by Minilab in cooperation with NMRAs. Three hundred and six samples were then tested fully in the laboratory, of which 74 were found to be non-compliant with a range of quality problems, from very minor non-compliance to absence of the API in two samples.

Quality survey of antituberculosis medicines in Eastern Europe (2009)

A quality survey of antituberculosis medicines focused on products containing rifampicin, isoniazid, kanamycin and ofloxacin was initiated in Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine and Uzbekistan; 291 samples were collected and testing is ongoing.

Several other quality monitoring projects had been conducted since 2005.

Training and capacity building

Training and capacity building were important components of the PQP with the aim of increasing the regulatory capacity of NMRAs in developing countries and to assist manufacturers, CROs and QC laboratories in these countries to improve standards and meet prequalification requirements.

Training was generally provided through seminars and workshops, and might include visits to manufacturers. It was based on prequalification and WHO requirements, but might also be problem-oriented, e.g. relating to a specific product type. NMRA staff and manufacturers frequently participated together in the same training programme and, where possible, the focus was on “train the trainer” for maximum effect.

Thirteen training sessions were organized or supported by WHO in 2007, 15 in 2008 and seven up to September 2009.

In addition to training activities, capacity building of regulatory authorities was supported by the programme hosting rotational posts for assessors in Geneva. These were available for periods of three months during which the participant worked alongside WHO experts and also attended the sessions in Copenhagen to learn from external international experts.

Technical assistance

Technical assistance might be provided to a specific manufacturer, which was committed to participation in the PQP, found to be capable and willing to improve, and was located in a developing country. The products manufactured were to be included in an EOI list, must be of high value for public health purposes and must be poorly represented on the list of prequalified medicines.

Expert consultants were provided by WHO to assist a manufacturer with compliance with GMP, GCP or GLP, as well as with data development and compilation of dossiers or regulatory guidance.

To avoid conflict of interest, technical assistance was independent from dossier assessments and inspections.

During 2008 technical assistance was provided to eight manufacturers.

Future challenges

Some of the key challenges facing the PQP were:

- motivating manufacturers to apply for prequalification and maintain prequalification, to ensure the continued supply of essential priority medicines;
- submission of incomplete or poor quality dossiers;
- non-compliance with GMP by all types of manufacturers;
- difficulty in filling technical positions within PQP;
- lack of availability of national experts (assessors and inspectors);
- reducing the total time taken to prequalify;
- an increasing demand for capacity building (shift from general to more specific technical training); and
- trust-building and information exchange to avoid duplication of effort.

The Committee was provided with an update on the PQP activities in 2009 and took note of the progress made.

9.2 Guidelines on requalification of prequalified dossiers

Section 12 (Maintenance of prequalification status) of WHO's *Procedure for prequalification of pharmaceutical products* (WHO Technical Report Series, No. 953, Annex 3, 2009) stated under "Maintenance of prequalification status" that:

"WHO will furthermore arrange for the products and manufacturing sites included in the list to be re-evaluated at regular intervals. If, as a result of this re-evaluation, it is found that a product and/or specified manufacturing site no longer complies with the WHO-recommended standards, such products and manufacturing sites will be removed from

the list. Failure of a manufacturer or applicant to participate in the re-evaluation procedure will also lead to removal from the list.

Re-evaluation, including re-inspections of manufacturing sites and CROs, would be done at regular intervals, based on risk assessment, but at least once every five years.

Re-evaluation, including re-inspections, should also be performed:

- if any fraud or omissions by the applicant, manufacturer(s) of an FPP or API, or CROs in the initial assessment procedure or during the follow-up activities, became evident; and
- if WHO or any United Nations agency considered that a batch or batches of supplied prequalified pharmaceutical products were not in compliance with the specifications which were found to be applicable upon prequalification.”

In order to define the documentation and information required from the applicants or manufacturers whereby the quality part of the prequalified product could be re-evaluated by WHO, a draft of the *Guidelines on the requalification of prequalified dossiers* had been developed by the quality assessors of the PQP.

These draft guidelines were circulated for comment and discussed at a meeting of the PQP assessment and inspector teams. The resulting revised draft was tabled and discussed at the consultation on WHO guidelines for medicines quality assurance, quality control laboratories and technology transfer in July 2009. At this meeting it was recommended that the document be tabled at the Expert Committee meeting for possible adoption. Following review during the consultation, the revised guidelines were once again circulated for comments.

The comments received were provided to the Committee in the form of a table.

Following discussion, the Expert Committee adopted these new guidelines (Annex 6).

9.3 **Guidelines for the preparation of a contract research organization master file**

WHO, PIC/S and several NMRAs recommended that manufacturers submit a site master file (SMF) for review when applying for registration of a medicine. An SMF is a document prepared by the manufacturer containing specific and factual GMP information about the production and/or control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations carried out in adjacent and nearby buildings. If only part of a pharmaceutical operation was carried out on

the site, the SMF needed to describe only those operations, e.g. analysis or packaging.

Some NMRAs were also inspecting clinical trials. Clinical trials were often conducted at CROs. During inspections at CROs by WHO prequalification inspectors it was observed that not all information regarding such CROs was available to inspectors when preparing for their inspections. In addition, in several cases, significant changes had been implemented by the CROs from the time of the conduct of a trial or bioequivalence study opposed to what was reflected in the study report. These included changes in key personnel, activities, and even location of the site. This often made inspections problematic as some of the core information regarding the site could no longer be verified.

After consultation with inspectors from NMRAs, sponsors and CROs, it was suggested that a document similar to the SMF would provide useful information in the preparation for an inspection, and for those responsible to review or perform a risk analysis when planning GCP or GLP inspections. The proposal of the establishment of a contract research organization master file (CROMF) was welcomed by all parties contacted. It could be seen as an extension of the existing recommendation for the SMF of a manufacturing facility.

An initial draft CROMF was prepared and circulated to specialists for initial comments. The comments were reviewed by the Secretariat and incorporated where appropriate. The draft was then widely circulated for comments, which were discussed and incorporated, after which the document was again widely circulated in line with the usual procedure.

The comments received were provided to the Expert Committee.

The Expert Committee took note of the update, reviewed the major comments received, and agreed and adopted the general principles. It furthermore agreed to the formation of a subgroup of specialists to review all comments in more detail and to prepare a new version of this working document for circulation to the Expert Committee members for ratification. This document was, therefore, adopted provided no major comments were received (Annex 7).

10. Nomenclature, terminology and databases

10.1 Quality assurance terminology

The update of the database, available on the WHO quality assurance web site (http://www.who.int/medicines/areas/quality_safety/quality_assurance/en/) was presented to the Committee, as well as a document

containing quality assurance terminology. The Expert Committee thanked the Secretariat for its work on the database and suggested making this information widely available.

In connection with the discussions during the WHO Governing Bodies' meetings, the issue of terminology for "counterfeit" and "substandard" medicines was raised.

Counterfeit medicines

Within the context of the work of the Expert Committee, definitions for "counterfeit medicines" were included in the glossaries of the following WHO guidelines (WHO Database on Quality Assurance: for updates see documents included in the meeting file and also on the Medicines web site: <http://www.who.int/medicines/services/expertcommittees/pharmprep/TermListcategory.pdf>).

In: WHO good distribution practices for pharmaceutical products (*fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*, WHO Technical Report Series, No. 937, 2006).

In: WHO Guidelines for inspection of drug distribution channels (*thirty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*, WHO Technical Report Series, No. 885, 1999).

In: WHO Guidelines on import procedures for pharmaceutical products (*thirty-fourth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*, WHO Technical Report Series, No. 863, 1996).

Within the context of the work of the IMPACT Annual Meeting held in December 2008 in Hammamet, Tunisia) and based on the work done by the IMPACT Working group on Legislative and Regulatory Infrastructure, a new definition had been developed and was available at: http://www.who.int/impact/resources/IMPACTthirdgeneralmeeting_%20report.pdf.

These definitions are included in the *Draft principles and elements for national legislation against counterfeit medical products* which has been circulated for comments.

The Expert Committee:

- took note of the above and suggested closely following the feedback received regarding the suggested IMPACT definition with a view to further discussion of the outcome during the next meeting of the Expert Committee; and
- recommended the preparation of an overview on the definitions used in the various international, regional and national contexts.

The importance of including NMRAs in this discussion was stressed as their expertise was needed to differentiate between the different issues. It was proposed that this discussion take place during the upcoming ICDRA in 2010.

“Substandard medicines”

Within the context of the work of this Expert Committee, no officially adopted definition currently existed for “substandard medicines”. As this question was raised frequently a “question and answer” had been introduced on the WHO web site as follows:

“What are substandard medicines?”

Substandard medicines (also called out-of-specification (OOS) products) are genuine medicines produced by manufacturers authorized by the NMRA which do not meet quality specifications set for them by national standards.

Normally, each medicine that a manufacturer produces has to comply with quality standards and specifications. These standards and specifications are reviewed and assessed by the NMRA before the product is authorized for marketing.”

The Expert Committee discussed the issue and agreed that there was a need for a definition. It suggested circulation of the proposal as amended during the meeting for comments within the usual consultative procedure.

10.2 International Nonproprietary Names

The Expert Committee was briefed on the activities of the International Nonproprietary Names (INN) Programme. In the past 11 years 1445 INN had been named. The Programme had developed an integrated data management system which would permit access from the Internet, allow worldwide multiusers, multiplatform application, with all the user tasks “integrated” within the process, standard and open-source technologies, secure and protected environment: confidentiality of data and process steps, electronic documentation at each step and track of each process step. The future steps for INN included the online INN Application, Report and Statistic Generator, offline use and integration with other databases.

10.3 Pharmacopoeial references

An update was given to the Expert Committee on the ongoing revision of the pharmacopoeial references and pharmacopoeia commission secretariats would be contacted. The updated references would be posted on the Medicines web site. The Committee welcomed this information being made available in its updated form.

11. Miscellaneous

11.1 WHO Model List of Essential Medicines

A paper presented by QSM (working document QAS/09.293/Rev.1) was discussed by the Expert Committee for the Selection and Use of Essential Medicines at its meeting in March 2009. The Expert Committee broadly endorsed the QSM proposals concerning:

- dosage form terminology; and
- expression of medicine strength.

The expanded Explanatory notes in the sixteenth edition of the WHO Model List of Essential Medicines (and in the second edition of the WHO Model List of Essential Medicines for Children) included a link to the Quality assurance area of the WHO Medicines web site and to the online text of the current edition of *The International Pharmacopoeia*. In addition, an Annex on dosage form terminology had been included. The Explanatory notes and Annex 1 (as published on the Medicines web site: http://www.who.int/selection_medicines/committees/expert/17/en/index.html) were presented to the Expert Committee on Specifications for Pharmaceutical Preparations for information.

With respect to the expression of medicines strengths, the Expert Committee for the Selection and Use of Essential Medicines agreed the principles that would be applied in future lists and requested its Secretariat to review the current entries and revise them accordingly. The principles were set out in the report of the Expert Committee; an extract from the unedited report, as made available on the WHO Medicines web site, was presented for information.

When revised in accordance with these principles, entries in cases where the API was not the active moiety would more clearly distinguish between:

- those for which the strength was expressed in terms of active moiety (the salt would be indicated in parentheses, e.g. “50 mg (as sodium salt)”)
- those for which the strength was expressed in terms of API (the salt would be given in full, e.g. “50 mg codeine phosphate”).

Where necessary, in instances of potential confusion (e.g. amodiaquine, quinine salts) a warning note would be included.

The Committee congratulated the Secretariat on its efforts to provide more clarity with regard to strengths and dosage form references within the Model List.

11.2 Update on stability

The revised working document on *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* was adopted by the Expert

Committee at its forty-third meeting after a long and intensive consultation process (see *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products*, Annex 2, WHO Technical Report Series, No. 953, 2009).

Appendix 1 included a *List of WHO Member States' required long-term stability conditions* as per information received from countries. Preference was given — based on the comments received from NMRAs — to providing “real” conditions required by national authorities. Completing the table for all WHO Member States proved to be a major challenge. However, thanks to IFPMA and special efforts made during and subsequent to the ICDRA meeting, the list could be completed. As a consequence the list comprised three different types of entries as follows.

Entries in bold type:

Information obtained through respective regional harmonization groups (e.g. Association of Southeast Asian Nations (ASEAN, ICH) and Gulf Cooperation Council (GCC)) and from official communications from NMRAs to WHO.

Entries in normal type:

Information collated during the 13th ICDRA in September 2008, from representatives of NMRAs.

Entries in italic type:

Information provided by IFPMA based on the references given in the guidelines.

Moreover, during and following the preparation of the Expert Committee report, the Secretariat actively contacted again, with the help of colleagues from the Medicines Regulatory Support Programme, those national authorities for which the entries were “informal” and/or in accordance with published studies.

The aim was to update the list on the Medicines web site upon receipt of confirmed new information from NMRAs. Any changes would be based on information received through official correspondence with accompanying reference to national guidance.

Detailed feedback was received from IFPMA regarding possible updates of the stability testing conditions for Afghanistan, Canada, Chile, India and Israel, as well as the labelling statements listed in Appendix 3 of the guidelines.

In accordance with the process described and suggested above for the update of the table in Appendix 1 of the stability guidelines, the Secretariat would, with the agreement of the Expert Committee:

- update the entry for Canada, as the official information had been received; and
- continue to contact the NMRAs of the other countries listed above with respect to the correctness of their entries.

As regards the proposal for the labelling information, intensive discussions were held on this topic during the consultation process. The final decision was to add the labelling statements in an Appendix as a recommendation. IFPMA might submit a concrete proposal which could be circulated for comments and discussed at the next Expert Committee meeting.

Implementation

Following the intense cooperation with the Quality Expert Working Groups within the ICH, the ICH web site included a new reference to the WHO stability guidelines as follows:

“Q1F: Stability Data Package for Registration Applications in Climatic Zones III and IV

➔ The ICH Steering Committee endorsed the withdrawal of the Q1F guideline at its meeting in Yokohama, June 2006 and decided to leave definition of storage conditions in Climatic Zones III and IV to the respective regions and WHO. [Click here to open the Explanatory Note and have access to the WHO Stability Guideline](#) in the electronic version of this report.”

The Expert Committee endorsed:

- that updates of long-term conditions required for marketing authorization in WHO Member States would be made as received from authorities; and
- the suggestion to include the details of this major harmonization effort and resolution of any possible further concerns during the ICDRA meeting to be held in Singapore in 2010.

11.3 Diethylene glycol

Over the years accidental or deliberate counterfeiting of medicines with diethylene glycol (DEG) had occurred many times and in many countries. The first recorded incident occurred in the USA in 1937. The episode killed a large number of Americans, mostly children. The latest incident happened in Nigeria where an equally large number of people were reported to have died. Beyond Nigeria the toxic chemical had caused mass poisoning in Argentina, Bangladesh, China, Haïti, India, Nigeria, Panama and South Africa. Numerous articles and references have referred to detected cases

of deaths due to DEG poisoning during the past decades. However, it was not known how many unreported deaths had actually occurred since some victims might have perished without visiting a health-care facility or seeing medical doctors.

Investigation of some of the above-mentioned incidents had revealed the main contributing factors for the incidents to be:

- absence of control by NMRAs of the manufacture, export and import of glycerol and propylene glycol;
- purchase of glycerol and propylene glycol by pharmaceutical manufacturers from unreliable sources or through brokers and traders; and
- lack of testing of the quality of glycerol and propylene glycol prior to using them in the manufacture of pharmaceutical products.

The above situation clearly showed that unless strict controls and safeguard measures were put in place by NMRAs, more people would fall victim to DEG poisoning.

Following up on the recurring incidents of DEG poisoning the Expert Committee discussed a proposal to send out a general alert to the NMRAs which should include recommendations to prevent such events in the future. Extensive discussion took place and the proposed text was amended to include further details. It was decided to form a small group to work out the final text. The Committee endorsed the proposal in general and agreed that the working group should submit the final text to the Committee members for final adoption.

12. **Summary and recommendations**

The Expert Committee on Specifications for Pharmaceutical Preparations provides recommendations and tools to assure the quality of medicines from their development phase to their final distribution to the patients. It advises the Director-General in the area of quality assurance of medicines.

This Expert Committee is looking back on a history of more than 60 years! The first meeting of the Expert Committee, named “Unification on Pharmacopoeias” at that time, was held in 1947. Since the inception of this WHO Expert Committee, its members have worked towards making available clear, independent and practical recommendations, written and physical standards, as well as international guidelines for quality medicines. Standards in the area of quality assurance for medicines are developed by the Committee through a wide international consensus building process. Detailed recommendations can be found under each relevant section in the report.

The activities discussed during this Expert Committee meeting have broad inter- and intracluster relationships and links. There are joint activities, specifically with the WHO Expert Committee on Biological Standardization, and on the Selection and Use of Essential Medicines and its Subcommittee on Medicines for Children. In addition, the Committee serves to develop specific additional guidance and specifications as needed for the various medicines recommended by WHO Programmes.

This Committee also serves the United Nations Programme on Prequalification of Medicines managed and operated by WHO, as the Programme could not function without the guidelines, standards and specifications adopted by this Committee after passage through its rigorous, international and wide consultative process. The advantage for the Committee is that, as a result of implementing these guidelines and specifications, practical suggestions for potential revision or on the need for additional guidance are communicated in return to the Expert Committee.

Regarding implementation from a wider perspective, the international guidelines, specifications and nomenclature developed under the aegis of this Committee serve all Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts, and underpin important initiatives, including the prequalification of medicines, the Roll Back Malaria Programme, Stop TB, essential medicines and medicines for children. The advice and recommendations provided by this Expert Committee are intended to help national and regional authorities and procurement agencies, as well as major international bodies and institutions, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and international organizations such as UNICEF — to combat circulation of substandard medicines and to work towards access to quality medicines.

In conclusion, the Expert Committee on Specifications for Pharmaceutical Preparations gives recommendations and provides independent international standards and guidelines in the area of quality assurance for implementation by WHO Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts, as well as WHO's medicines' related programmes and initiatives. Making resources available for these activities is, therefore, very cost-effective.

The following new guidelines were adopted and recommended for use:

- WHO good practices for pharmaceutical quality control laboratories (Annex 1)
- WHO good manufacturing practices for active pharmaceutical ingredients (Annex 2)
- WHO good manufacturing practices for pharmaceutical products containing hazardous substances (Annex 3)

- WHO good manufacturing practices for sterile pharmaceutical products (Annex 4)
- WHO good distribution practices for pharmaceutical products (Annex 5)
- Guidelines on the requalification of prequalified dossiers (Annex 6)
- Guidelines for the preparation of a contract research organization master file (Annex 7)

For inclusion in *The International Pharmacopoeia*

The following monographs were adopted:

- *For antiretroviral medicines*
 - Lopinavir
 - Tenofovir disoproxil fumarate
 - Indinavir capsules
 - Saquinavir tablets
 - Tenofovir tablets
 - Lopinavir and ritonavir tablets
 - Efavirenz
- *For antimalarial medicines*
 - Amodiaquine tablets
 - Artesunate
 - Artesunate tablets
 - Quinine bisulfate tablets
 - Quinine sulfate tablets
- *For antituberculosis medicines*
 - Amikacin
 - Amikacin sulfate
 - Amikacin injection
 - Kanamycin monosulfate
 - Kanamycin acid sulfate
 - Kanamycin injection
- *For radiopharmaceuticals*
 - Iobenguane (^{131}I) injection
 - Samarium ethylene diamine tetramethylene phosphonate complex (^{153}Sm) injection
 - Sodium iodide (^{131}I) capsules
 - Sodium iothalamate (^{125}I) injection
 - Sodium phosphate (^{32}P) injection
 - Strontium chloride (^{89}Sr) injection
 - Technetium ($^{99\text{m}}\text{Tc}$) bicisate complex injection
 - Technetium ($^{99\text{m}}\text{Tc}$) exametazime complex injection
 - Technetium ($^{99\text{m}}\text{Tc}$) mebrofenin complex injection

- Technetium (^{99m}Tc) mertiatide injection
- Technetium (^{99m}Tc) succimer complex injection
- Technetium (^{99m}Tc) sulfur colloid injection
- Technetium (^{99m}Tc) tetrofosmin complex injection
- Technetium (^{99m}Tc) tin colloidal injection
- Technetium (^{99m}Tc) pyrophosphate tin complex injection
- Technetium (^{99m}Tc) methylene diphosphonate (MDP) complex injection
- Technetium (^{99m}Tc) sestamibi complex injection
- Yttrium silicate (^{90}Y) colloid injection
- *Other medicines*
 - Mebendazole
 - Oseltamivir phosphate
 - Oxytocin
 - Oxytocin injection
- *General monographs for*
 - Tablets
 - Capsules
- *General policy topics and general revision issues for*
 - Monographs title and strengths
 - Strengths available statement
 - Identity tests
 - Polymorphism

Adoption of new International Chemical Reference Substances

- Carbidopa
- Colchicine
- Lumefantrine
- DL-Methionine
- Naloxone hydrochloride
- Oseltamivir phosphate for system suitability
- Oseltamivir phosphate

And the following replacements

- Artemisinin
- Prednisone

The following recommendations were made in the various quality assurance-related areas. Progress on the suggested actions should be reported to the Expert Committee at its next meeting.

The underlying principle is that the development of specifications and guidelines will be carried out using the established international consultative process.

The International Pharmacopoeia

- Continue development of specifications for medicines in accordance with the work plan revised and adopted at this meeting.
- Continue the efforts of international collaboration in relation to the revision and inclusion of general methods and new monographs for excipients.
- Continue the preparatory work on the supplements to *The International Pharmacopoeia*, 4th edition and towards the 5th edition, especially in electronic form (CD-ROM and online).

International Chemical Reference Substances (ICRS)

- Continue promoting the use of ICRS through various activities, including a promotional offer to national authorities and improvements of the ICRS web site.

External Quality Assurance Assessment Scheme

- Continue the External Quality Assurance Assessment Scheme (EQAAS) for pharmaceutical quality control laboratories with a new phase 5.

Good practices for pharmaceutical microbiology laboratories

- Continue the consultation process through preparation of a new text on good practices for pharmaceutical microbiology laboratories.

Good manufacturing practices (GMP) and manufacture

- Follow up on the revision process for GMP for biologicals currently being undertaken under the aegis of the Expert Committee on Biological Standardization.
- Follow up on development of the WHO guidelines on GMP for blood establishments currently being undertaken under the aegis of the Expert Committee on Biological Standardization and ensure that these new guidelines also be sent for comment to the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.
- Initiate the consultation process for a revision of the main principles of GMP, considering inclusion of the quality unit concept, quality risk management and product quality review.
- Initiate a revision process as identified for some paragraphs of the GMP for heating, ventilation and air-conditioning (HVAC).
- Review and initiate an update of the WHO guidelines on Hazard Analysis and Critical Control Points (HACCP) to cover new trends in quality risk management.

Transfer of technology

- Continue the development of the *WHO guidelines on transfer of technology*, giving special consideration to keeping the balance between GMP and business criteria, including the concept of quality by design and the possibility of optional requirements depending on the type of transfer.

WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce

- Continue the steps to be taken regarding the *WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce* in consultation with WHO Member States and the WHO Legal Counsel.
- Post the revised “Questions and Answers” on the functioning of the Scheme on the revised document on the WHO web site and include it in *WHO Drug Information*, with the possibility of receiving comments and reviewing any question(s) that might raise major concerns.

Good distribution practices (GDP) for pharmaceutical products

Follow up on development of the WHO guidelines on regulatory oversight on pharmaceutical cold chain management. Harmonized guidance for the storage and transport of temperature-sensitive pharmaceutical products is currently being developed under the aegis of the Expert Committee on Biological Standardization. Ensure that these new guidelines are also sent for comment to the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and to the IMPACT working group that developed the revision of the GDP.

Regulatory guidance

- Continue the consultation process and advancement of the *Development of paediatric medicines: pharmaceutical development. Points to consider*.
- Continue the development of the *Pharmaceutical development for multisource (generic) pharmaceutical products*.
- Continue updating the long-term stability testing requirements for marketing authorization in WHO Member States as received from authorities.
- Follow up on the recurring incidents of DEG poisoning, prepare a proposal for a general alert to the NMRAs, including recommendations to prevent such events in the future.

Quality assurance terminology

- Make the updated database on quality assurance terminology widely available.

- Provide feedback from the Circular Letter mailed to all Member States regarding the terminology used within the national legislation for “counterfeit medicines” or equivalent terms used, with a view to further discussion of the outcome during the next meeting of the Expert Committee and possibly during the ICDRA.
- Circulate a proposal for a new definition for “substandard medicines” as discussed during the meeting.

Pharmacopoeia references

- Post an update of the references and contact details for national, regional and international pharmacopoeias on the Medicines Quality Assurance web site.

WHO databases

- Maintain the consolidated database on nomenclature used in WHO quality assurance.
- Maintain the INN database and continue to make it available on the web site.

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Annex 1

WHO good practices for pharmaceutical quality control laboratories

General considerations

Glossary

Part one. Management and infrastructure

1. Organization and management
2. Quality management system
3. Control of documentation
4. Records
5. Data-processing equipment
6. Personnel
7. Premises
8. Equipment, instruments and other devices
9. Contracts

Part two. Materials, equipment, instruments and other devices

10. Reagents
11. Reference substances and reference materials
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Appendix

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

General considerations

The WHO Expert Committee on Specifications for Pharmaceutical Products adopted in 1999 the guidelines entitled *WHO Good practices for national pharmaceutical control laboratories*, which were published as Annex 3 of the WHO Technical Report Series, No. 902, 2002. As the other guidelines related to laboratory quality assurance have been updated and subsequent inspections for the compliance with the guidelines on good practices for national pharmaceutical control laboratories indicated that some sections were in need of improvement and clarification, it was considered necessary to prepare a revised text.

These guidelines provide advice on the quality management system within which the analysis of active pharmaceutical ingredients (APIs), excipients and pharmaceutical products should be performed to demonstrate that reliable results are obtained.

Compliance with the recommendations provided in these guidelines will help promote international harmonization of laboratory practices and will facilitate cooperation among laboratories and mutual recognition of results.

Special attention should be given to ensure the correct and efficient functioning of the laboratory. Planning and future budgets should ensure that the necessary resources are available inter alia for the maintenance of the laboratory, as well as for an appropriate infrastructure and energy supply. Means and procedures should be in place (in case of possible supply problems) to ensure that the laboratory can continue its activities.

These guidelines are applicable to any pharmaceutical quality control laboratory, be it national, commercial or nongovernmental. However, they do not include guidance for those laboratories involved in the testing of biological products, e.g. vaccines and blood products. Separate guidance for such laboratories is available.

These guidelines are consistent with the requirements of the *WHO guidelines for good manufacturing practices (1)* and with the requirements of the International Standard ISO/IEC 17025:2005 (2), and provide detailed guidance for laboratories performing quality control of medicines. The guidance specific to microbiology laboratories can be found in the draft working document *WHO guideline on good practices for pharmaceutical microbiology laboratories* (reference QAS/09.297).

The good practice outlined below is to be considered as a general guide and it may be adapted to meet individual needs provided that an equivalent level of quality assurance is achieved. The notes given provide clarification of the text or examples; they do not contain requirements which should be fulfilled to comply with these guidelines.

Pharmaceutical quality control testing is usually a matter of repetitive testing of samples of APIs or of a limited number of pharmaceutical products, whereas national quality control laboratories have to be able to deal with a much wider range of pharmaceutical substances and products and, therefore, have to apply a wider variety of test methods. Specific recommendations for national pharmaceutical quality control laboratories are addressed in the following text. Particular consideration is given to countries with limited resources wishing to establish a governmental pharmaceutical quality control laboratory, having recently done so, or which are planning to modernize an existing laboratory.

Quality control laboratories may perform some or all quality control activities, e.g. sampling, testing of APIs, excipients, packaging materials and/or pharmaceutical products, stability testing, testing against specifications and investigative testing.

For the quality of a medicine sample to be correctly assessed:

- The submission of a sample of an API, excipient or pharmaceutical product or a suspected counterfeit material to the laboratory, selected in accordance with national requirements, should be accompanied by a statement of the reason why the analysis has been requested.
- The analysis should be correctly planned and meticulously executed.
- The results should be competently evaluated to determine whether the sample complies with the specifications or other relevant criteria.

National pharmaceutical quality control laboratories

The government, normally through the national medicines regulatory authority (NMRA), may establish and maintain a pharmaceutical quality control laboratory to carry out the required tests and assays to verify that APIs, excipients and pharmaceutical products meet the prescribed specifications. Large countries may require several pharmaceutical quality control laboratories which conform to national legislation, and appropriate arrangements should, therefore, be in place to monitor their compliance with a quality management system. Throughout the process of marketing authorization and postmarketing surveillance, the laboratory or laboratories work closely with the NMRA.

A national pharmaceutical quality control laboratory provides effective support for an NMRA acting together with its inspection services. The analytical results obtained should accurately describe the properties of the samples assessed, permitting correct conclusions to be drawn about the quality of the samples of medicines analysed, and also serving as an adequate basis for any subsequent administrative regulations and legal action.

National pharmaceutical quality control laboratories usually encompass essentially two types of activity:

- compliance testing of APIs, pharmaceutical excipients and pharmaceutical products employing “official” methods including pharmacopoeial methods, validated analytical procedures provided by the manufacturer and approved by the relevant government authority for marketing authorization or validated analytical procedures developed by the laboratory; and
- investigative testing of suspicious, illegal, counterfeit substances or products, submitted for examination by medicine inspectors, customs or police.

To ensure patient safety, the role of the national pharmaceutical quality control laboratory should be defined in the general pharmaceutical legislation of the country in such a way that the results provided by it can, if necessary, lead to enforcement of the law and legal action.

Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

acceptance criterion for an analytical result

Predefined and documented indicators by which a result is considered to be within the limit(s) or to exceed the limit(s) indicated in the specification.

accuracy

The degree of agreement of test results with the true value or the closeness of the results obtained by the procedure to the true value (*1*).

Note: It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure. It is generally acceptable to use a “spiked” placebo which contains a known quantity or concentration of a reference substance.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body (*1*).

analytical test report

An analytical test report usually includes a description of the test procedure(s) employed, results of the analysis, discussion and conclusions and/or recommendations for one or more samples submitted for testing (see Part three, sections 18.7–18.11).

analytical worksheet

A printed form, an analytical workbook or electronic means (e-records) for recording information about the sample, as well as reagents and solvents used, test procedure applied, calculations made, results and any other relevant information or comments (see Part three, section 15).

batch (or lot)

A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches which are later brought together to form a final homogeneous batch. In the case of terminal sterilization the batch size is determined by the capacity of the autoclave. In continuous manufacture the batch should correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval (1).

batch number (or lot number)

A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis (1).

calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established (1).

certificate of analysis

The list of test procedures applied to a particular sample with the results obtained and the acceptance criteria applied. It indicates whether or not the sample complies with the specification (3).

certified reference material

Reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides

the value of the specified property, its associated uncertainty and a statement of metrological traceability (4).

compliance testing

Analysis of active pharmaceutical ingredients (APIs), pharmaceutical excipients, packaging material or pharmaceutical products according to the requirements of a pharmacopoeial monograph or a specification in an approved marketing authorization.

control sample

A sample used for testing the continued accuracy and precision of the procedure. It should have a matrix similar to that of the samples to be analysed. It has an assigned value with its associated uncertainty.

design qualification (DQ)

Documented collection of activities that define the functional and operational specifications of the instrument and criteria for selection of the vendor, based on the intended purpose of the instrument.

Note: Selection and purchase of a new instrument should follow a conscious decision process, based on the needs of the technical management. When designing a new laboratory facility, the design specification and the requirements for services should be agreed between the management team and the agreed suppliers and documented.

good manufacturing practice(s) (GMP)

That part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization (1).

installation qualification (IQ)

The performance of tests to ensure that the analytical equipment used in a laboratory is correctly installed and operates in accordance with established specifications.

management review

A formal, documented review of the key performance indicators of a quality management system performed by top management.

manufacturer

A company that carries out operations such as production, packaging, testing, repackaging, labelling and/or relabelling of pharmaceuticals (1).

marketing authorization (product licence, registration certificate)

A legal document issued by the competent medicines regulatory authority that authorizes the marketing or free distribution of a pharmaceutical product in the respective country after evaluation for safety, efficacy and quality. In terms of quality it establishes inter alia the detailed composition and formulation of the pharmaceutical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labelling, storage conditions, shelf-life and approved conditions of use.

measurement uncertainty

Non-negative parameter characterizing the dispersion of quantity values being attributed to a measurand (analyte), based on the information used (4).

metrological traceability

Property of a measurement result whereby the result can be related to a reference through a documented, unbroken chain of calibrations, each contributing to the measurement uncertainty (4).

operational qualification (OQ)

Documented verification that the analytical equipment performs as intended over all anticipated operating ranges.

out-of-specification (OOS) result

All test results that fall outside the specifications or acceptance criteria established in product dossiers, drug master files, pharmacopoeias or by the manufacturer (5).

performance qualification (PQ)

Documented verification that the analytical equipment operates consistently and gives reproducibility within the defined specifications and parameters for prolonged periods.

pharmaceutical excipient

A substance, other than the active pharmaceutical ingredient (API), which has been appropriately evaluated for safety and is included in a medicines delivery system to:

- aid in the processing of the medicines delivery system during its manufacture;
- protect, support or enhance stability, bioavailability or patient acceptability;
- assist in pharmaceutical product identification; or
- enhance any other attribute of the overall safety and effectiveness of the medicine during its storage or use (6, 7).

pharmaceutical product

Any material or product intended for human or veterinary use, presented in its finished dosage form or as a starting material for use in such a dosage form, which is subject to control by pharmaceutical legislation in the exporting state and/or the importing state (1).

precision

The degree of agreement among individual results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. Precision, usually expressed as relative standard deviation, may be considered at three levels: repeatability (precision under the same operating conditions over a short period of time), intermediate precision (within laboratory variations — different days, different analysts or different equipment) and reproducibility (precision between laboratories).

primary reference substance (or standard)

A substance that is widely acknowledged to possess the appropriate qualities within a specified context, and whose assigned content is accepted without requiring comparison with another chemical substance (8).

Note: Pharmacopoeial chemical reference substances are considered to be primary reference substances. In the absence of a pharmacopoeial reference substance, a manufacturer should establish a primary reference substance.

qualification of equipment

Action of proving and documenting that any analytical equipment complies with the required specifications and performs suitably for its intended purpose (see Part two, section 12).

quality control

All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

quality management system

An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality (see Part one, section 2).

quality manager

A member of staff who has a defined responsibility and authority for ensuring that the management system related to quality is implemented and followed at all times (see Part one, section 1.3(j)).

quality manual

A handbook that describes the various elements of the quality management system for assuring the quality of the test results generated by a laboratory (see Part one, sections 2.1–2.2).

quality unit(s)

An organizational unit, independent of production, which fulfils both quality assurance and quality control responsibilities. This can be in the form of separate quality assurance and quality control or a single individual or group, depending on the size and structure of the organization.

reference material

Material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process (4).

reference substance (or standard)

An authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use (8).

secondary reference substance (or standard)

A substance whose characteristics are assigned and/or calibrated by comparison with a primary reference substance. The extent of characterization and testing of a secondary reference substance may be less than for a primary reference substance (8).

Note: Often referred to as an “in-house” working standard.

signature (signed)

Record of the individual who performed a particular action or review. The record can be initials, full handwritten signature, personal seal or authenticated and secure electronic signature.

specification

A list of detailed requirements (acceptance criteria for the prescribed test procedures) with which the substance or pharmaceutical product has to conform to ensure suitable quality.

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations both general and specific.

standard uncertainty

Uncertainty of the result of a measurement expressed as a standard deviation (4, 9, 10).

system suitability test

A test which is performed to ensure that the analytical procedure fulfils the acceptance criteria which had been established during the validation of the procedure. This test is performed before starting the analytical procedure and is to be repeated regularly, as appropriate, throughout the analytical run to ensure that the system's performance is acceptable at the time of the test.

validation of an analytical procedure

The documented process by which an analytical procedure (or method) is demonstrated to be suitable for its intended use.

verification of an analytical procedure

Process by which a pharmacopoeial method or validated analytical procedure is demonstrated to be suitable for the analysis to be performed.

verification of performance

Test procedure regularly applied to a system (e.g. liquid chromatographic system) to demonstrate consistency of response.

Part One. Management and infrastructure

1. Organization and management

- 1.1 The laboratory, or the organization of which it is part, should be an entity that is legally authorized to function and can be held legally responsible.
- 1.2 The laboratory should be organized and operate so as to meet the requirements laid down in these guidelines.
- 1.3 The laboratory should:
 - (a) have managerial and technical personnel with the authority and resources needed to carry out their duties and to identify the occurrence of departures from the quality management system or the procedures for performing tests and/or calibrations, validation and verification, and to initiate actions to prevent or minimize such departures;
 - (b) have arrangements to ensure that its management and personnel are not subject to commercial, political, financial and other

pressures or conflicts of interest that may adversely affect the quality of their work;

- (c) have a policy and procedure in place to ensure confidentiality of
 - information contained in marketing authorizations,
 - transfer of results or reports,
 - and to protect data in archives (paper and electronic);
- (d) define, with the aid of organizational charts, the organization and management structure of the laboratory, its place in any parent organization (such as the ministry or the NMRA in the case of a national pharmaceutical quality control laboratory), and the relationships between management, technical operations, support services and the quality management system;
- (e) specify the responsibility, authority and interrelationships of all personnel who manage, perform or verify work which affects the quality of the tests and/or calibrations, validations and verifications;
- (f) ensure the precise allocation of responsibilities, particularly in the designation of specific units for particular types of medicines;
- (g) nominate trained substitutes/deputies for key management and specialized scientific personnel;
- (h) provide adequate supervision of staff, including trainees, by persons familiar with the test and/or calibration, validation and verification methods and procedures, as well as their purpose and the assessment of the results;
- (i) have management which has overall responsibility for the technical operations and the provision of resources needed to ensure the required quality of laboratory operations;
- (j) designate a member of staff as quality manager who, irrespective of other duties he/she may have, will ensure compliance with the quality management system. The nominated quality manager should have direct access to the highest level of management at which decisions are taken on laboratory policies or resources;
- (k) ensure adequate information flow between staff at all levels. Staff are to be made aware of the relevance and importance of their activities;
- (l) ensure the traceability of the sample from receipt, throughout the stages of testing, to the completion of the analytical test report;
- (m) maintain an up-to-date collection of all specifications and related documents (paper or electronic) used in the laboratory; and
- (n) have appropriate safety procedures (see Part four).

- 1.4 The laboratory should maintain a registry with the following functions:
- (a) receiving, distributing and supervising the consignment of the samples to the specific units; and
 - (b) keeping records on all incoming samples and accompanying documents.
- 1.5 In a large laboratory, it is necessary to guarantee communication and coordination between the staff involved in the testing of the same sample in different units.

2. **Quality management system**

- 2.1 The laboratory or organization management should establish, implement and maintain a quality management system appropriate to the scope of its activities, including the type, range and volume of testing and/or calibration, validation and verification activities it undertakes. The laboratory management should ensure that its policies, systems, programmes, procedures and instructions are described to the extent necessary to enable the laboratory to assure the quality of the test results that it generates. The documentation used in this quality management system should be communicated, available to, and understood and implemented by, the appropriate personnel. The elements of this system should be documented, e.g. in a quality manual, for the organization as a whole and/or for a laboratory within the organization.

Note: Quality control laboratories of a manufacturer may have this information in other documents than a quality manual.

- 2.2 The quality manual should contain as a minimum:
- (a) a quality policy statement, including at least the following:
 - (i) a statement of the laboratory management's intentions with respect to the standard of service it will provide,
 - (ii) a commitment to establishing, implementing and maintaining an effective quality management system,
 - (iii) the laboratory management's commitment to good professional practice and quality of testing, calibration, validation and verification,
 - (iv) the laboratory management's commitment to compliance with the content of these guidelines,
 - (v) a requirement that all personnel concerned with testing and calibration activities within the laboratory familiarize themselves with the documentation concerning quality and

the implementation of the policies and procedures in their work;

- (b) the structure of the laboratory (organizational chart);
- (c) the operational and functional activities pertaining to quality, so that the extent and the limits of the responsibilities are clearly defined;
- (d) outline of the structure of documentation used in the laboratory quality management system;
- (e) the general internal quality management procedures;
- (f) references to specific procedures for each test;
- (g) information on the appropriate qualifications, experience and competencies that personnel are required to possess;
- (h) information on initial and in-service training of staff;
- (i) a policy for internal and external audit;
- (j) a policy for implementing and verifying corrective and preventive actions;
- (k) a policy for dealing with complaints;
- (l) a policy for performing management reviews of the quality management system;
- (m) a policy for selecting, establishing and approving analytical procedures;
- (n) a policy for handling of OOS results;
- (o) a policy for the employment of appropriate reference substances and reference materials;
- (p) a policy for participation in appropriate proficiency testing schemes and collaborative trials and the evaluation of the performance (applicable to national pharmaceutical quality control laboratories, but may be applied by other laboratories); and
- (q) a policy to select service providers and suppliers.

2.3 The laboratory should establish, implement and maintain authorized written SOPs including, but not limited to, administrative and technical operations, such as:

- (a) personnel matters, including qualifications, training, clothing and hygiene;
- (b) the change control;
- (c) internal audit;
- (d) dealing with complaints;
- (e) implementation and verification of corrective and preventive actions;
- (f) the purchase and receipt of consignments of materials (e.g. samples, reagents);

- (g) the procurement, preparation and control of reference substances and reference materials (8);
- (h) the internal labelling, quarantine and storage of materials;
- (i) the qualification of equipment (11);
- (j) the calibration of equipment;
- (k) preventive maintenance and verification of instruments and equipment;
- (l) sampling, if performed by the laboratory, and visual inspection;
- (m) the testing of samples with descriptions of the methods and equipment used;
- (n) atypical and OOS results;
- (o) validation of analytical procedures;
- (p) cleaning of laboratory facilities, including bench tops, equipment, work stations, clean rooms (aseptic suites) and glassware;
- (q) monitoring of environmental conditions, e.g. temperature and humidity;
- (r) monitoring storage conditions;
- (s) disposal of reagents and solvent samples; and
- (t) safety measures.

2.4 The activities of the laboratory should be systematically and periodically audited (internally and, where appropriate, by external audits or inspections) to verify compliance with the requirements of the quality management system and to apply corrective and preventive actions, if necessary. The audits should be carried out by trained and qualified personnel, who are independent of the activity to be audited. The quality manager is responsible for planning and organizing internal audits addressing all elements of the quality management system. Such audits should be recorded, together with details of any corrective and preventive action taken.

2.5 Management review of quality issues should be regularly undertaken (at least annually), including:

- (a) reports on internal and external audits or inspections and any follow-up required to correct any deficiencies;
- (b) the outcome of investigations carried out as a result of complaints received, doubtful (atypical) or aberrant results reported in collaborative trials and/or proficiency tests; and
- (c) corrective actions applied and preventive actions introduced as a result of these investigations.

3. **Control of documentation**

3.1 Documentation is an essential part of the quality management system. The laboratory should establish and maintain procedures

to control and review all documents (both internally generated and from external sources) that form part of the quality documentation. A master list identifying the current version status and distribution of documents should be established and readily available.

3.2 The procedures should ensure that:

- (a) each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation;
- (b) appropriate, authorized SOPs are available at the relevant locations, e.g. near instruments;
- (c) documents are kept up to date and reviewed as required;
- (d) any invalid document is removed and replaced with the authorized, revised document with immediate effect;
- (e) a revised document includes references to the previous document;
- (f) old, invalid documents are retained in the archives to ensure traceability of the evolution of the procedures; any copies are destroyed;
- (g) all relevant staff are trained for the new and revised SOPs; and
- (h) quality documentation, including records, is retained for a minimum of five years.

3.3 A system of change control should be in place to inform staff of new and revised procedures. The system should ensure that:

- (a) revised documents are prepared by the initiator, or a person who performs the same function, reviewed and approved at the same level as the original document and subsequently released by the quality manager (quality unit); and
- (b) staff acknowledge by a signature that they are aware of applicable changes and their date of implementation.

4. **Records**

4.1 The laboratory should establish and maintain procedures for the identification, collection, indexing, retrieval, storage, maintenance and disposal of and access to all quality and technical/scientific records.

4.2 All original observations, including calculations and derived data, calibration, validation and verification records and final results, should be retained on record for an appropriate period of time in accordance with national regulations and, if applicable, contractual arrangements, whichever is longer. The records should include the data recorded in the analytical worksheet by the technician or analyst

on consecutively numbered pages with references to the appendices containing the relevant recordings, e.g. chromatograms and spectra. The records for each test should contain sufficient information to permit the tests to be repeated and/or the results to be recalculated, if necessary. The records should include the identity of the personnel involved in the sampling, preparation and testing of the samples. The records of samples to be used in legal proceedings should be kept according to the legal requirements applicable to them.

Note: The generally accepted retention period of shelf-life plus one year for a pharmaceutical product on the market and 15 years for an investigational product is recommended, unless national regulations are more stringent or contractual arrangements do not require otherwise.

- 4.3 All quality and technical/scientific records (including analytical test reports, certificates of analysis and analytical worksheets) should be legible, readily retrievable, stored and retained within facilities that provide a suitable environment that will prevent modification, damage or deterioration and/or loss. The conditions under which all original records are stored should be such as to ensure their security and confidentiality and access to them should be restricted to authorized personnel. Electronic storage and signatures may also be employed but with restricted access and in conformance with requirements for electronic records (12–16).
- 4.4 Quality management records should include reports from internal (and external if performed) audits and management reviews, as well as records of all complaints and their investigations, including records of possible corrective and preventive actions.

5. **Data-processing equipment**

- 5.1 Detailed recommendations are provided in Appendix 5 to Annex 4 of the *Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*: Supplementary guidelines in good manufacturing practice: validation. Validation of computerized systems (12).
- 5.2 For computers, automated tests or calibration equipment, and the collection, processing, recording, reporting, storage or retrieval of test and/or calibration data, the laboratory should ensure that:
 - (a) computer software developed by the user is documented in sufficient detail and appropriately validated or verified as being suitable for use;

- (b) procedures are established and implemented for protecting the integrity of data. Such procedures should include, but are not limited to, measures to ensure the integrity and confidentiality of data entry or collection and the storage, transmission and processing of data. In particular, electronic data should be protected from unauthorized access and an audit trail of any amendments should be maintained;
- (c) computers and automated equipment are maintained so as to function properly and are provided with the environmental and operating conditions necessary to ensure the integrity of test and calibration data;
- (d) procedures are established and implemented for making, documenting and controlling changes to information stored in computerized systems; and
- (e) electronic data should be backed up at appropriate regular intervals according to a documented procedure. Backed-up data should be retrievable and stored in such a manner as to prevent data loss.

Note: For further guidance on validation of data-processing equipment, refer to documents published by the International Society for Pharmaceutical Engineering (13, 14), US Food and Drug Administration (15), European Commission (16) and the Official Medicines Control Laboratories Network of the Council of Europe (17).

6. Personnel

- 6.1 The laboratory should have sufficient personnel with the necessary education, training, technical knowledge and experience for their assigned functions.
- 6.2 The technical management should ensure the competence of all personnel operating specific equipment, instruments or other devices, who are performing tests and/or calibrations, validations or verifications. Their duties also involve the evaluation of results as well as signing analytical test reports and certificates of analysis (see Part three, sections 18.7–18.11 and 19).
- 6.3 Staff undergoing training should be appropriately supervised and should be assessed on completion of the training. Personnel performing specific tasks should be appropriately qualified in terms of their education, training and experience, as required.
- 6.4 The laboratory personnel should be permanently employed or under contract. The laboratory should ensure that additional technical and key support personnel who are under contract are supervised and

sufficiently competent and that their work is in accordance with the quality management system.

- 6.5 The laboratory should maintain current job descriptions for all personnel involved in tests and/or calibrations, validations and verifications. The laboratory should also maintain records of all technical personnel, describing their qualifications, training and experience.
- 6.6 The laboratory should have the following managerial and technical personnel:
- (a) a head of laboratory (supervisor), who should have qualifications appropriate to the position, with extensive experience in medicines analysis and laboratory management in a pharmaceutical quality control laboratory in the regulatory sector or in industry. The head of laboratory is responsible for the content of certificates of analysis and analytical testing reports. This person is also responsible for ensuring that:
 - (i) all key members of the laboratory staff have the requisite competence for the required functions and their grades reflect their responsibilities,
 - (ii) the adequacy of existing staffing, management and training procedures is reviewed periodically,
 - (iii) the technical management is adequately supervised;
 - (b) the technical management who ensure that:
 - (i) procedures for performing calibration, verification and (re-) qualification of instruments, monitoring of environmental and storage conditions are in place and are conducted as required,
 - (ii) regular in-service training programmes to update and extend the skills of both professionals and technicians are arranged,
 - (iii) the safekeeping of any materials subject to poison regulation or to the controls applied to narcotic and psychotropic substances (see Part one, section 7.12) kept in the workplace is under the supervision of an authorized person,
 - (iv) national pharmaceutical quality control laboratories regularly participate in suitable proficiency testing schemes and collaborative trials to assess analytical procedures or reference substances;
 - (c) analysts, who should normally be graduates in pharmacy, analytical chemistry, microbiology or other relevant subjects,

- with the requisite knowledge, skills and ability to adequately perform the tasks assigned to them by management and to supervise technical staff;
- (d) technical staff, who should hold diplomas in their subjects awarded by technical or vocational schools; and
 - (e) a quality manager (see Part one, section 1.3(j)).

7. Premises

- 7.1 The laboratory facilities are to be of a suitable size, construction and location. These facilities are to be designed to suit the functions and operations to be conducted in them. Rest and refreshment rooms should be separate from laboratory areas. Changing areas and toilets should be easily accessible and appropriate for the number of users.
- 7.2 The laboratory facilities should have adequate safety equipment located appropriately and measures should be in place to ensure good housekeeping. Each laboratory should be equipped with adequate instruments and equipment, including work benches, work stations and fume hoods.
- 7.3 The environmental conditions, including lighting, energy sources, temperature, humidity and air pressure, are to be appropriate to the functions and operations to be performed. The laboratory should ensure that the environmental conditions are monitored, controlled and documented and do not invalidate the results or adversely affect the quality of the measurements.
- 7.4 Special precautions should be taken and, if necessary, there should be a separate and dedicated unit or equipment (e.g. isolator, laminar flow work bench) to handle, weigh and manipulate highly toxic substances, including genotoxic substances. Procedures should be in place to avoid exposure and contamination.
- 7.5 Archive facilities should be provided to ensure the secure storage and retrieval of all documents. The design and condition of the archives should be such as to protect the contents from deterioration. Access to the archives should be restricted to designated personnel.
- 7.6 Procedures should be in place for the safe removal of types of waste including toxic waste (chemical and biological), reagents, samples, solvents and air filters.
- 7.7 Microbiological testing, if performed, should be contained in an appropriately designed and constructed laboratory unit. For further guidance see the draft working document *WHO guideline on good*

practices for pharmaceutical microbiology laboratories (reference QAS/09.297).

- 7.8 If in vivo biological testing (e.g. rabbit pyrogen test) is included in the scope of the laboratory activities then the animal houses should be isolated from the other laboratory areas with a separate entrance and air-conditioning system. The relevant guidance and regulations are to be applied (18).

Laboratory storage facilities

- 7.9 The storage facilities should be well organized for the correct storage of samples, reagents and equipment.
- 7.10 Separate storage facilities should be maintained for the secure storage of samples, retained samples (see Part three, section 20), reagents and laboratory accessories (see Part two, sections 10.13–10.14), reference substances and reference materials (see Part two, section 11). Storage facilities should be equipped to store material, if necessary, under refrigeration (2–8°C) and frozen (-20°C) and securely locked. All specified storage conditions should be controlled, monitored and records maintained. Access should be restricted to designated personnel.
- 7.11 Appropriate safety procedures should be drawn up and rigorously implemented wherever toxic or flammable reagents are stored or used. The laboratory should provide separate rooms or areas for storing flammable substances, fuming and concentrated acids and bases, volatile amines and other reagents, such as hydrochloric acid, nitric acid, ammonia and bromine. Self-igniting materials, such as metallic sodium and potassium, should also be stored separately. Small stocks of acids, bases and solvents may be kept in the laboratory store but the main stocks of these items should preferably be retained in a store separate from the laboratory building.
- 7.12 Reagents subject to poison regulations or to the controls applied to narcotic and psychotropic substances should be clearly marked as required by national legislation. They should be kept separately from other reagents in locked cabinets. A designated responsible member of staff should maintain a register of these substances. The head of each unit should accept personal responsibility for the safekeeping of any of these reagents kept in the workplace.
- 7.13 Gases also should be stored in a dedicated store, if possible isolated from the main building. Wherever possible gas bottles in the laboratory are to be avoided and distribution from an external gas

store is preferred. If gas bottles are present in the laboratory they should be safely secured.

Note: Consideration should be given to the installation of gas generators.

8. **Equipment, instruments and other devices**

- 8.1 Equipment, instruments and other devices should be designed, constructed, adapted, located, calibrated, qualified, verified and maintained as required by the operations to be carried out in the local environment. The user should purchase the equipment from an agent capable of providing full technical support and maintenance when necessary.
- 8.2 The laboratory should have the required test equipment, instruments and other devices for the correct performance of the tests and/or calibrations, validations and verifications (including the preparation of samples and the processing and analysis of test and/or calibration data).
- 8.3 Equipment, instruments and other devices, including those used for sampling, should meet the laboratory's requirements and comply with the relevant standard specifications, as well as being verified, qualified and/or calibrated regularly (see Part two, section 12).

9. **Contracts**

Purchasing services and supplies

- 9.1 The laboratory should have a procedure for the selection and purchasing of services and supplies it uses that affect the quality of testing.
- 9.2 The laboratory should evaluate suppliers of critical consumables, supplies and services which affect quality of testing, maintain records of these evaluations and list approved suppliers, which have been demonstrated to be of a suitable quality with respect to the requirements of the laboratory.

Subcontracting of testing

- 9.3 When a laboratory subcontracts work, which may include specific testing, it is to be done with organizations approved for the type of activity required. The laboratory is responsible for periodically assessing the competence of a contracted organization.
- 9.4 When a laboratory performs testing for a customer and subcontracts part of the testing, it should advise the customer of the arrangement in writing and, if appropriate, gain his or her approval.

- 9.5 There should be a written contract which clearly establishes the duties and responsibilities of each party, defines the contracted work and any technical arrangements made in connection with it. The contract should permit the laboratory to audit the facilities and competencies of the contracted organization and ensure the access of the laboratory to records and retained samples.
- 9.6 The contracted organization should not pass to a third party any work entrusted to it under contract without the laboratory's prior evaluation and approval of the arrangements.
- 9.7 The laboratory should maintain a register of all subcontractors that it uses and a record of the assessment of the competence of subcontractors.
- 9.8 The laboratory takes the responsibility for all results reported, including those furnished by the subcontracting organization.

Part two. Materials, equipment, instruments and other devices

10. Reagents

- 10.1 All reagents and chemicals, including solvents and materials used in tests and assays, should be of appropriate quality.
- 10.2 Reagents should be purchased from reputable, approved suppliers and should be accompanied by the certificate of analysis, and the material safety data sheet, if required.
- 10.3 In the preparation of reagent solutions in the laboratory:
 - (a) responsibility for this task should be clearly specified in the job description of the person assigned to carry it out; and
 - (b) prescribed procedures should be used which are in accordance with published pharmacopoeial or other standards where available. Records should be kept of the preparation and standardization of volumetric solutions.
- 10.4 The labels of all reagents should clearly specify:
 - (a) content;
 - (b) manufacturer;
 - (c) date received and date of opening of the container;
 - (d) concentration, if applicable;
 - (e) storage conditions; and
 - (f) expiry date or retest date, as justified.

10.5 The labels of reagent solutions prepared in the laboratory should clearly specify:

- (a) name;
- (b) date of preparation and initials of technician or analyst;
- (c) expiry date or retest date, as justified; and
- (d) concentration, if applicable.

10.6 The labels for volumetric solutions prepared in the laboratory should clearly specify:

- (a) name;
- (b) molarity (or concentration);
- (c) date of preparation and initials of technician/analyst;
- (d) date of standardization and initials of technician/analyst; and
- (e) standardization factor.

Note: The laboratory should ensure that the volumetric solution is suitable for use at the time of use.

10.7 In the transportation and subdivision of reagents:

- (a) whenever possible they should be transported in the original containers; and
- (b) when subdivision is necessary, clean containers should be used and appropriately labelled.

Visual inspection

10.8 All reagent containers should be visually inspected to ensure that the seals are intact, both when they are delivered to the store and when they are distributed to the units.

10.9 Reagents that appear to have been tampered with should be rejected; however, this requirement may exceptionally be waived if the identity and purity of the reagent concerned can be confirmed by testing.

Water

10.10 Water should be considered as a reagent. The appropriate grade for a specific test should be used as described in the pharmacopoeias or in an approved test when available.

10.11 Precautions should be taken to avoid contamination during its supply, storage and distribution.

10.12 The quality of the water should be verified regularly to ensure that the various grades of water meet the appropriate specifications.

Storage

- 10.13 Stocks of reagents should be maintained in a store under the appropriate storage conditions (ambient temperature, under refrigeration or frozen). The store should contain a supply of clean bottles, vials, spoons, funnels and labels, as required, for dispensing reagents from larger to smaller containers. Special equipment may be needed for the transfer of larger volumes of corrosive liquids.
- 10.14 The person in charge of the store is responsible for looking after the storage facilities and their inventory and for noting the expiry date of chemicals and reagents. Training may be needed in handling chemicals safely and with the necessary care.

11. Reference substances and reference materials

- 11.1 Reference substances (primary reference substances or secondary reference substances (8)) are used for the testing of a sample.

Note: Pharmacopoeial reference substances should be employed when available and appropriate for the analysis. When a pharmacopoeia reference substance has not been established then the manufacturer should use its own reference substance.

- 11.2 Reference materials may be necessary for the calibration and/or qualification of equipment, instruments or other devices.

Registration and labelling

- 11.3 An identification number should be assigned to all reference substances, except for pharmacopoeial reference substances.
- 11.4 A new identification number should be assigned to each new batch.
- 11.5 This number should be marked on each vial of the reference substance.
- 11.6 The identification number should be quoted on the analytical worksheet every time the reference substance is used (see Part three, section 15.5). In the case of pharmacopoeial reference substances the batch number and/or the batch validity statement should be attached to the worksheet.
- 11.7 The register for all reference substances and reference materials should be maintained and contain the following information:
- (a) the identification number of the substance or material;
 - (b) a precise description of the substance or material;
 - (c) the source;

- (d) the date of receipt;
 - (e) the batch designation or other identification code;
 - (f) the intended use of the substance or material (e.g. as an infrared reference substance or as an impurity reference substance for thin-layer chromatography);
 - (g) the location of storage in the laboratory, and any special storage conditions;
 - (h) any further necessary information (e.g. the results of visual inspections);
 - (i) expiry date or retest date;
 - (j) certificate (batch validity statement) of a pharmacopoeial reference substance and a certified reference material which indicates its use, the assigned content, if applicable, and its status (validity); and
 - (k) in the case of secondary reference substances prepared and supplied by the manufacturer, the certificate of analysis.
- 11.8 A person should be nominated to be responsible for reference substances and reference materials.
- 11.9 If a national pharmaceutical quality control laboratory is required to establish reference substances for use by other institutions, a separate reference substances unit should be established.
- 11.10 In addition a file should be kept in which all information on the properties of each reference substance is entered including the safety data sheets.
- 11.11 For reference substances prepared in the laboratory, the file should include the results of all tests and verifications used to establish the reference substances and expiry date or retest date; these should be signed by the responsible analyst.

Retesting (monitoring)

- 11.12 All reference substances prepared in the laboratory or supplied externally should be retested at regular intervals to ensure that deterioration has not occurred. The interval for retesting depends on a number of factors, including stability of the substance, storage conditions employed, type of container and extent of use (how often the container is opened and closed). More detailed information on the handling, storage and retesting of reference substances is given in the *WHO General guidelines for the establishment, maintenance and distribution of chemical reference substances* (8).
- 11.13 The results of these tests should be recorded and signed by the responsible analyst.

- 11.14 In the case that the result of retesting of a reference substance is non-compliant, a retrospective check of tests performed using this reference substance since its previous examination should be carried out. For evaluation of outcomes of retrospective checks and consideration of possible corrective actions, risk analysis should be applied.
- 11.15 Pharmacopoeial reference substances are regularly retested and the validity (current status) of these reference substances is available from the issuing pharmacopoeia by various means, e.g. web sites or catalogues. Retesting by the laboratory is not necessary, provided the reference substances are stored in accordance with the storage conditions indicated.

12. **Calibration, verification of performance and qualification of equipment, instruments and other devices**

- 12.1 Each item of equipment, instrument or other device used for testing, verification and/or calibration should, when practicable, be uniquely identified.
- 12.2 All equipment, instruments and other devices (e.g. volumetric glassware and automatic dispensers) requiring calibration should be labelled, coded or otherwise identified to indicate the status of calibration and the date when recalibration is due.
- 12.3 Laboratory equipment should undergo design qualification, installation qualification, operation qualification and performance qualification (for definitions of these terms see the Glossary) (11). Depending on the function and operation of the instrument, the design qualification of a commercially available standard instrument may be omitted as the installation qualification, operational qualification and performance qualification may be considered to be a sufficient indicator of its suitable design.
- 12.4 As applicable, the performance of equipment should be verified at appropriate intervals according to a plan established by the laboratory.
- 12.5 Measuring equipment should be regularly calibrated according to a plan established by the laboratory (11).
- 12.6 Specific procedures should be established for each type of measuring equipment, taking into account the type of equipment, the extent of use and supplier's recommendations. For example:
- pH meters are verified with standard certified buffer solutions before use;

- balances are to be checked daily using internal calibration and regularly using suitable test weights, and requalification should be performed annually using certified reference weights.

- 12.7 Only authorized personnel should operate equipment, instruments and devices. Up-to-date SOPs on the use, maintenance, verification, qualification and calibration of equipment, instruments and devices (including any relevant manuals provided by the manufacturer) should be readily available for use by the appropriate laboratory personnel together with a schedule of the dates on which verification and/or calibration is due.
- 12.8 Records should be kept of each item of equipment, instrument or other device used to perform testing, verification and/or calibration. The records should include at least the following:
- (a) the identity of the equipment, instrument or other device;
 - (b) the manufacturer's name and the equipment model, serial number or other unique identification;
 - (c) the qualification, verification and/or calibration required;
 - (d) the current location, where appropriate;
 - (e) the equipment manufacturer's instructions, if available, or an indication of their location;
 - (f) the dates, results and copies of reports, verifications and certificates of all calibrations, adjustments, acceptance criteria and the due date of the next qualification, verification and/or calibration;
 - (g) the maintenance carried out to date and the maintenance plan; and
 - (h) a history of any damage, malfunction, modification or repair.

It is also recommended that records should be kept and additional observations made of the time for which the equipment, instruments or devices were used.

- 12.9 Procedures should include instructions for the safe handling, transport and storage of measuring equipment. On reinstallation, requalification of the equipment is required to ensure that it functions properly.
- 12.10 Maintenance procedures should be established, e.g. regular servicing should be performed by a team of maintenance specialists, whether internal or external, followed by verification of performance.
- 12.11 Equipment, instruments and other devices, either subjected to overloading or mishandling, giving suspect results, shown to be defective or outside specified limits, should be taken out of service and clearly labelled or marked. Wherever possible they should not be used until they have been repaired and requalified.

- 12.12 When the equipment, instruments and other devices are outside the direct control of the laboratory for a certain period or have undergone major repair, the laboratory should requalify the equipment to ensure its suitability for use.

Note: For further guidance on calibration, verification of performance and qualification of equipment refer to:

- *Procedures for verifying and calibrating refractometers, thermometers used in determinations of melting temperatures and potentiometers for pH determinations and methods for verifying the reliability of scales for ultraviolet and infrared spectrophotometers and spectrofluorometers in The International Pharmacopoeia (19);*
- *Specific guidelines for qualification of equipment elaborated by the European Network of Official Medicines Control Laboratories (OMCL) (20); and*
- *General chapter of the US Pharmacopeia on Analytical instrument qualification (21).*

13. **Traceability**

- 13.1 The result of an analysis should be traceable, when appropriate, ultimately to a primary reference substance.
- 13.2 All calibrations or qualification of instruments should be traceable to certified reference materials and to SI units (metrological traceability).

Part Three. Working procedures

14. **Incoming samples**

Sections 14.1–14.3 are applicable to national pharmaceutical quality control laboratories.

- 14.1 Samples received by a laboratory may be for compliance testing or for investigative testing. Samples for compliance testing include routine samples for control, samples suspected of not complying with the specifications or samples submitted in connection with a marketing authorization process. Close collaboration with the providers of the samples is important. In particular it is important that the sample is large enough to enable, if required, a number of replicate tests to be carried out (see Part three, section 14.3) and for part of the sample to be retained (see Part three, section 20).

- 14.2 Samples for investigative testing may be submitted by various sources including customs, police and medicines inspectors. These samples comprise suspicious, illegal or counterfeit substances or products. Usually, the primary objective of investigative testing is to identify the substance or the ingredient in the product and, if sufficient substance or product is available, to estimate the purity or content. Well-documented screening procedures should be in place as well as confirmatory analytical procedures to positively identify the substance or the ingredient(s). If an estimation of the content of an identified ingredient is required then an appropriate quantitative analytical procedure should be applied. The value obtained should be reported with an indication of the uncertainty of measurement if required (see Part three, section 18.10).
- 14.3 It is common for a sample to be taken and divided into three approximately equal portions for submission to the laboratory:
- one for immediate testing;
 - the second for confirmation of testing if required; and
 - the third for retention in case of dispute.
- 14.4 If the laboratory is responsible for sampling of substances, materials or products for subsequent testing then it should have a sampling plan and an internal procedure for sampling available to all analysts and technicians working in the laboratory. Samples should be representative of the batches of material from which they are taken and sampling should be carried out so as to avoid contamination and other adverse effects on quality, or mix-up of or by the material being sampled. All the relevant data related to sampling should be recorded.

Note: Guidelines for sampling of pharmaceutical products and related materials were adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-ninth meeting (22).

Test request

- 14.5 A standard test request form should be filled out and should accompany each sample submitted to the laboratory. In the case of a pharmaceutical manufacturer's laboratory the requirements may be given in the master production instructions.
- 14.6 The test request form should provide or leave space for the following information:
- (a) the name of the institution or inspector that supplied the sample;
 - (b) the source of the material;

- (c) a full description of the medicine, including its composition, international nonproprietary name (INN) (if available) and brand name(s);
- (d) dosage form and concentration or strength, the manufacturer, the batch number (if available) and the marketing authorization number;
- (e) the size of the sample;
- (f) the reason for requesting the analysis;
- (g) the date on which the sample was collected;
- (h) the size of the consignment from which it was taken, when appropriate;
- (i) the expiry date (for pharmaceutical products) or retest date (for APIs and pharmaceutical excipients);
- (j) the specification to be used for testing;
- (k) a record of any further comments (e.g. discrepancies found or associated hazard); and
- (l) the required storage conditions.

14.7 The laboratory should review the test request to ensure that:

- (a) the requirements are adequately defined and the laboratory has the capability and resources to meet them; and
- (b) the appropriate tests and/or methods are selected and are capable of meeting customers' requirements.

Any issue should be resolved with the originator of the request for analysis before testing starts and a record of the review should be kept.

Registration and labelling

14.8 All newly delivered samples and accompanying documents (e.g. the test request) should be assigned a registration number. Separate registration numbers should be assigned to requests referring to two or more medicines, different dosage forms, or different batches of the same medicine or different sources of the same batch. If applicable, a unique registration number should also be assigned to any incoming retained sample (see Part three, section 20).

14.9 A label bearing the registration number should be affixed to each container of the sample. Care should be taken to avoid obscuring any other markings or inscriptions.

14.10 A register should be kept, which may be a record book, a card file or data-processing equipment, in which the following information is recorded:

- (a) the registration number of the sample;
- (b) the date of receipt; and
- (c) the specific unit to which the sample was forwarded.

Visual inspection of the submitted sample

14.11 The sample received should be visually inspected by laboratory staff to ensure that the labelling conforms with the information contained in the test request. The findings should be recorded, dated and signed. If discrepancies are found, or if the sample is obviously damaged, this fact should be recorded without delay on the test request form. Any queries should be immediately referred back to the provider of the sample.

Storage

14.12 The sample prior to testing, the retained sample (see Part three, section 20) and any portions of the sample remaining after performance of all the required tests should be stored safely, taking into account the storage conditions (22, 23) specified for the sample.

Forwarding to testing

- 14.13 The specific unit to which the sample is sent for testing is determined by the person responsible.
- 14.14 The examination of a sample should not be started before the relevant test request has been received.
- 14.15 The sample should be properly stored until all relevant documentation has been received.
- 14.16 A request for analysis may be accepted verbally only in emergencies. All details should immediately be placed on record pending the receipt of written confirmation.
- 14.17 Unless a computerized system is used, copies or duplicates of all documentation should accompany each numbered sample when sent to the specific unit.
- 14.18 Testing should be performed as described under Part three, section 17.

15. Analytical worksheet

15.1 The analytical worksheet is an internal document to be used by the analyst for recording information about the sample, the test procedure, calculations and the results of testing. It is to be complemented by the raw data obtained in the analysis.

Purpose

- 15.2 The analytical worksheet contains documentary evidence either:
- to confirm that the sample being examined is in accordance with the requirements; or
 - to support an OOS result (see Part three, sections 18.1–18.3).

Use

- 15.3 A separate analytical worksheet should usually be used for each numbered sample or group of samples.
- 15.4 Analytical worksheets from different units relating to the same sample should be assembled together.

Content

- 15.5 The analytical worksheet should provide the following information:
- (a) the registration number of the sample (see Part three, section 14.9);
 - (b) page numbering, including the total number of pages (and including annexes);
 - (c) the date of the test request;
 - (d) the date on which the analysis was started and completed;
 - (e) the name and signature of the analyst;
 - (f) a description of the sample received;
 - (g) references to the specifications and a full description of test methods by which the sample was tested, including the limits;
 - (h) the identification of the test equipment used (see Part two, section 12.1);
 - (i) the identification number of any reference substance used (see Part two, section 11.5);
 - (j) if applicable, the results of the system suitability test;
 - (k) the identification of reagents and solvents employed;
 - (l) the results obtained;
 - (m) the interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), approved and signed by the supervisor; and
 - (n) any further comments, for example, for internal information (see Part three, section 17.1), or detailed notes on the specifications selected and the methods of assessment used (see Part three, section 15.9), or any deviation from the prescribed procedure, which should be approved and reported, or whether and when portions of the sample were forwarded to other units for special tests and the date on which the results were received.

- 15.6 All values obtained from each test, including blank results, should immediately be entered on the analytical worksheet and all graphical data, whether obtained from recording instruments or plotted by hand, should be attached or be traceable to an electronic record file or document where the data are available.
- 15.7 The completed analytical worksheet should be signed by the responsible analyst(s), verified and approved and signed by the supervisor.
- 15.8 When a mistake is made in an analytical worksheet or when data or text need to be amended, the old information should be deleted by putting a single line through it (it should not be erased or made illegible) and the new information added alongside. All such alterations should be signed by the person making the correction and the date of the change inserted. The reason for the change should also be given on the worksheet (suitable procedures should be in place for amending electronic worksheets).

Selection of the specifications to be used

- 15.9 The specification necessary to assess the sample may be that given in the test request or master production instructions. If no precise instruction is given, the specification in the officially recognized national pharmacopoeia may be used or, failing this, the manufacturer's officially approved or other nationally recognized specification. If no suitable method is available:
- (a) the specification contained in the marketing authorization or product licence may be requested from the marketing authorization holder or manufacturer and verified by the laboratory; or
 - (b) the requirements may be set by the laboratory itself on the basis of published information and any procedure employed is to be validated by the testing laboratory (see Part three, section 16).
- 15.10 For official specifications the current version of the relevant pharmacopoeia should be available.

Filing

- 15.11 The analytical worksheet should be kept safely together with any attachments, including calculations and recordings of instrumental analyses.

16. Validation of analytical procedures

- 16.1 All analytical procedures employed for testing should be suitable for the intended use. This is demonstrated by validation (24). Validation

also serves to establish acceptance criteria for system suitability tests which are subsequently employed for the verification of the analytical procedure before analysis.

- 16.2 Validation should be performed according to a validation protocol, which includes analytical performance characteristics to be verified for various types of analytical procedures. Typical characteristics which should be considered are listed in Table 1 (in the development phase of an analytical procedure, robustness, i.e. the ability of the procedure to provide results of acceptable accuracy and precision under a variety of conditions should also be considered). The results are to be documented in the validation report.

Table 1

Characteristics to consider during validation of analytical procedures

Type of analytical Procedure	Identification	Testing for impurities		Assay
		Quantitative tests	Limit tests	
				• dissolution (measurement only) • content/potency
Characteristics				
Accuracy	–	+	–	+
Precision				
Repeatability	–	+	–	+
Intermediate precision ^a	–	+	–	+
Specificity	+	+	+	+
Detection limit	–	– ^b	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– Characteristic is normally not evaluated; + characteristic should normally be evaluated.

^a In cases where a reproducibility study has been performed, intermediate precision is not needed.

^b May be needed in some cases.

- 16.3 Pharmacopoeial methods are considered to be validated for the intended use as prescribed in the monograph(s). However, the laboratory should also confirm that, for example, for a particular finished pharmaceutical product (FPP) examined for the first time, no interference arises from the excipients present, or that for an API, impurities coming from a new route of synthesis are adequately differentiated. If the pharmacopoeial method is adapted for another use then it should be validated for such a use to demonstrate that it is fit-for-purpose.

- 16.4 System suitability testing is an integral part of many analytical procedures. The tests are based on the fact that the equipment, electronics, analytical operations and samples to be analysed contribute to the system. Which system suitability tests are to be applied depends on the type of procedure to be used. System suitability tests are employed for the verification of pharmacopoeial methods or validated analytical procedures and should be performed prior to the analysis. Provided the system suitability criteria are fulfilled the method or procedure is considered to be suitable for the intended purpose.

Note: If a large number of samples is being analysed in sequence, then appropriate system suitability tests are to be performed throughout the sequence to demonstrate that the performance of the procedure is satisfactory.

Verification is not required for basic pharmacopoeial methods such as (but not limited to) pH, loss on drying and wet chemical methods.

- 16.5 A major change to the analytical procedure, or in the composition of the product tested, or in the synthesis of the API, will require revalidation of the analytical procedure.

Note: Further guidance on validation of analytical procedures is available in the following:

- *Guideline elaborated by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (25);*
- *Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL) (26);*
- *General chapters of the US Pharmacopeia on Validation of compendial procedures and on Verification of compendial procedures (27).*

17. Testing

- 17.1 The sample should be tested in accordance with the work plan of the laboratory after completion of the preliminary procedures. If this is not feasible the reasons should be noted, e.g. in the analytical worksheet (see Part three, section 15), and the sample should be stored in a special place which is kept locked (see Part three, section 14.12).
- 17.2 Specific tests required may need to be carried out by another unit or by a specialized external laboratory (see Part one, section 9). The responsible person should prepare the request and arrange for the

transfer of the required number of units (bottles, vials or tablets) from the sample. Each of these units should bear the correct registration number. When the analytical test report contains results of tests performed by subcontractors, these results should be identified as such.

- 17.3 Detailed guidance on official pharmacopoeial requirements is usually given in the general notices and specific monographs of the pharmacopoeia concerned. Test procedures should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner. Where system suitability criteria are defined in the method they should be fulfilled. Any deviation from the test procedure should be approved and documented.

18. **Evaluation of test results**

- 18.1 Test results should be reviewed and, where appropriate, evaluated statistically after completion of all the tests to determine whether they are mutually consistent and if they meet the specifications used. The evaluation should take into consideration the results of all the tests (all test data). Whenever doubtful (atypical) results are obtained they should be investigated. The complete testing procedure needs to be checked according to the internal quality management system (see also Part one, section 2).
- 18.2 When a doubtful result (suspected OOS result) has been identified, a review of the different procedures applied during the testing process is to be undertaken by the supervisor with the analyst or technician before retesting is permitted. The following steps should be followed:
- (a) confirm with the analyst or technician that the appropriate procedure(s) was (were) applied and followed correctly;
 - (b) examine the raw data to identify possible discrepancies;
 - (c) check all calculations;
 - (d) check that the equipment used was qualified and calibrated, and that system suitability tests were performed and were acceptable;
 - (e) ensure that the appropriate reagents, solvents and reference substances were used;
 - (f) confirm that the correct glassware was used; and
 - (g) ensure that original sample preparations are not discarded until the investigation is complete.
- 18.3 The identification of an error which caused an aberrant result will invalidate the result and a retest of the sample will be necessary.

Doubtful results can be rejected only if they are clearly due to an identified error. Sometimes the outcome of the investigation is inconclusive — no obvious cause can be identified — in which case a confirmatory determination is to be performed by another analyst who should be at least as experienced and competent in the analytical procedure as the original analyst. A similar value would indicate an OOS result. However, further confirmation using another validated method, if available, may be advised.

- 18.4 An SOP should be in place for the conduct of an investigation of an OOS test result. The SOP should give clear guidance on the number of retests allowed (based on sound statistical principles). All investigations and their conclusions should be recorded. In the event of an error, any corrective action taken and any preventive measure introduced should be recorded and implemented.
- 18.5 All individual results (all test data) with acceptance criteria should be reported.
- 18.6 All conclusions should be entered on the analytical worksheet (see Part three, section 15) by the analyst and signed by the supervisor.

Note: Further guidance on evaluation and reporting of test results is available in the following:

- *Guideline elaborated by the US Food and Drug Administration (5);*
- *Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL) (28).*

Analytical test report

- 18.7 The analytical test report is a compilation of the results and states the conclusions of the examination of a sample. It should be:
 - (a) issued by the laboratory; and
 - (b) based on the analytical worksheet (see Part three, section 15).
- 18.8 Any amendments to the original analytical test report will require the issue of a new corrected document.
- 18.9 Pharmacopoeial content limits are set taking into account the uncertainty of measurement, and the production capability and acceptance criteria for an analytical result should be predefined. Under presently applicable rules neither the pharmacopoeias nor the NMRAs require the value found to be expressed with its associated expanded uncertainty for compliance testing. However, when reporting the results of investigative testing, although the primary objective is to identify a substance in the sample, a determination of

its concentration may be also requested, in which case the estimated uncertainty should also be given.

18.10 Measurement uncertainty can be estimated in a number of ways, e.g.:

- (a) by preparing an uncertainty budget for each uncertainty component identified in an analytical procedure (bottom-up approach);
- (b) from validation data and control charts (29); and
- (c) from the data obtained from proficiency tests or collaborative trials (top-down approach).

Note: Further guidance can be found in various guidelines (9, 10, 30, 31, 32).

Content of the analytical test report

18.11 The analytical test report should provide the following information:

- (a) the laboratory registration number of the sample;
- (b) the laboratory test report number;
- (c) the name and address of the laboratory testing the sample;
- (d) the name and address of the originator of the request for analysis;
- (e) the name, description and batch number of the sample, where appropriate;
- (f) an introduction giving the background to and the purpose of the investigation;
- (g) a reference to the specifications used for testing the sample or a detailed description of the procedures employed (sample for investigative testing), including the limits;
- (h) the results of all the tests performed or the numerical results with the standard deviation of all the tests performed (if applicable);
- (i) a discussion of the results obtained;
- (j) a conclusion as to whether or not the sample(s) was (were) found to be within the limits of the specifications used, or for a sample for investigative testing, the substance(s) or ingredient(s) identified;
- (k) the date on which the test(s) was (were) completed;
- (l) the signature of the head of the laboratory or authorized person;
- (m) the name and address of the original manufacturer and, if applicable, those of the repacker and/or trader;
- (n) whether or not the sample(s) complies (comply) with the requirements;
- (o) the date on which the sample was received;
- (p) the expiry date or retest date, if applicable; and

- (q) a statement indicating that the analytical test report, or any portion thereof, cannot be reproduced without the authorization of the laboratory.

19. **Certificate of analysis**

19.1 A certificate of analysis is prepared for each batch of a substance or product and usually contains the following information:

- (a) the registration number of the sample;
- (b) date of receipt;
- (c) the name and address of the laboratory testing the sample;
- (d) the name and address of the originator of the request for analysis;
- (e) the name, description and batch number of the sample where appropriate;
- (f) the name and address of the original manufacturer and, if applicable, those of the repacker and/or trader;
- (g) the reference to the specification used for testing the sample;
- (h) the results of all tests performed (mean and standard deviation, if applicable) with the prescribed limits;
- (i) a conclusion as to whether or not the sample was found to be within the limits of the specification;
- (j) expiry date or retest date if applicable;
- (k) date on which the test(s) was (were) completed; and
- (l) the signature of the head of laboratory or other authorized person.

Note: The *Guideline on model certificate of analysis* was adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-sixth meeting (3).

20. **Retained samples**

20.1 Samples should be retained as required by the legislation or by the originator of the request for analysis. There should be a sufficient amount of retained sample to allow at least two re-analyses. The retained sample should be kept in its final pack.

Part four. Safety

21. **General rules**

21.1 General and specific safety instructions reflecting identified risk, should be made available to each staff member and supplemented regularly as appropriate (e.g. with written material, poster displays, audiovisual material and occasional seminars).

- 21.2 General rules for safe working in accordance with national regulations and SOPs normally include the following requirements:
- (a) safety data sheets should be available to staff before testing is carried out;
 - (b) smoking, eating and drinking in the laboratory should be prohibited;
 - (c) staff should be familiar with the use of fire-fighting equipment, including fire extinguishers, fire blankets and gas masks;
 - (d) staff should wear laboratory coats or other protective clothing, including eye protection;
 - (e) special care should be taken, as appropriate, in handling, for example, highly potent, infectious or volatile substances;
 - (f) highly toxic and/or genotoxic samples should be handled in a specially designed facility to avoid the risk of contamination;
 - (g) all containers of chemicals should be fully labelled and include prominent warnings (e.g. “poison”, “flammable”, “radioactive”) whenever appropriate;
 - (h) adequate insulation and spark-proofing should be provided for electrical wiring and equipment, including refrigerators;
 - (i) rules on safe handling of cylinders of compressed gases should be observed and staff should be familiar with the relevant colour identification codes;
 - (j) staff should be aware of the need to avoid working alone in the laboratory; and
 - (k) first-aid materials should be provided and staff instructed in first-aid techniques, emergency care and the use of antidotes.
- 21.3 Protective clothing should be available, including eye protection, masks and gloves. Safety showers should be installed. Rubber suction bulbs should be used on manual pipettes and siphons. Staff should be instructed in the safe handling of glassware, corrosive reagents and solvents and particularly in the use of safety containers or baskets to avoid spillage from containers. Warnings, precautions and instructions should be given for work with violent, uncontrollable or dangerous reactions when handling specific reagents (e.g. mixing water and acids, or acetone–chloroform and ammonia), flammable products, oxidizing or radioactive agents and especially biologicals such as infectious agents. Peroxide-free solvents should be used. Staff should be aware of methods for the safe disposal of unwanted corrosive or dangerous products by neutralization or deactivation and of the need for safe and complete disposal of mercury and its salts.
- 21.4 Poisonous or hazardous products should be singled out and labelled appropriately, but it should not be taken for granted that all other

chemicals and biologicals are safe. Unnecessary contact with reagents, especially solvents and their vapours, should be avoided. The use of known carcinogens and mutagens as reagents should be limited or totally excluded if required by national regulations. Replacement of toxic solvents and reagents by less toxic materials or reduction of their use should always be the aim, particularly when new techniques are developed.

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 - PA/PH/OMCL (07) 11 DEF CORR — Annex 3: Qualification of UV-visible spectrophotometers (http://www.edqm.eu/medias/fichiers/Annex_3_Qualification_of_UV_Visible_spectrophotometers.pdf),
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Appendix

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

A list of equipment considered by the Committee to be adequate either for a first-stage or medium-sized pharmaceutical quality control laboratory is given in the table. In the case of a medium-sized laboratory, specific sections are devoted to a microbiology unit and pharmacognosy/phytochemistry unit. For a first-stage laboratory testing herbal medicines, the additional equipment recommended is specified in the table.

This list does not represent any requirements which should be fulfilled to comply with these guidelines. NMRAs or laboratories wishing to perform pharmaceutical analyses may consider the following list in the establishment or upgrading of their testing facilities. For budgetary reasons it is necessary, besides the cost of equipment, to take into consideration the cost of reference materials, reagents, solvents, glassware, other laboratory commodities and personnel. Experience has shown that for sustainability, a laboratory should allow a margin of 10–15% per year of the purchasing expenditure on equipment to cover the cost of maintenance.

Table

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

First-stage laboratory	
<i>Equipment and major instruments</i>	<i>Quantity</i>
Top-loading balance	1
Analytical balance (5 digits)	1 or 2
Melting-point apparatus	1
pH meter (with assorted electrodes)	1
Microscope	1
Polarimeter	1
High-performance liquid chromatograph with ultraviolet detector	2
Ultraviolet/visible spectrophotometer	1
Infrared spectrophotometer with pellet press	1
Karl Fischer titrator (semi-micro determination of water)	1
Agate mortar with pestle	1
Equipment for thin-layer chromatography	1
Thin-layer chromatography spotter	1
Developing chambers	6 + 1 ^a
Atomizers	6

First-stage laboratory (cont.)	
Ultraviolet viewing lamp	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution apparatus	1
Soxhlet extraction apparatus (60 ml)	3 + 1 ^a
Micrometer callipers	1
Pycnometers	2
Burettes/pipettes (10 ml and 25 ml/1, 2, 5, 10, 20, 25, 50 ml)	3 of each
Desiccator	1 + 1 ^a
Centrifuge (table-top model, 4-place swing rotor)	1
Water-bath (20 litres)	1
Hot plates with magnetic stirrers	3
Vacuum pump (rotary, oil)	1
Drying oven (60 litres)	1
Vacuum oven (17 litres)	1
Muffle furnace	1
Refrigerator (explosion-proof)	1
Water distilling apparatus (8 litres/hour)	1
Water deionizer (10 litres/hour)	1
Dehumidifier (where needed)	1
Fume hood	1
Optional items	
Analytical microbalance	1
Flame photometer (including air compressor)	1
Refractometer	1
Viscometer	1
Vortex mixer	1
Shaker (wrist-action)	1
Pipette rinser	1
Constant temperature water-bath	1
Ultrasonic cleaner (5 litres)	1
Medium-sized laboratory	
Equipment and major instruments	Quantity
Top-loading balance	1 or 2
Analytical balance (5 digits)	2
Analytical microbalance	1

Medium-sized laboratory (cont.)	
Microscope	1 or 2
Equipment for thin-layer chromatography	1
Thin-layer chromatography multispotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1
Potentiometric titrimer	1
Micro-Kjeldahl equipment (including fume flasks)	1
Soxhlet extraction apparatus (60 ml)	3
Pycnometers	2
Burettes/pipettes (10 ml and 25 ml/1, 2, 5, 10, 20, 25, 50 ml)	6 of each
Micrometer callipers	1
Heating mantles for flasks (assorted sizes: 50, 200 and 2000 ml)	6
Sieves (assorted sizes)	1 set
Centrifuge (floor model)	1
Shaker (wrist-action)	1
Vortex mixers	2
Water-bath (electrical, 20 litres)	2 or 3
Hot plates with magnetic stirrers	3 or 4
Vacuum pump (rotary, oil)	2
Vacuum rotary evaporator	1
Drying oven (60 litres)	2 or 3
Muffle furnace (23 litres)	1
Vacuum oven (17 litres)	1
Desiccators	2
Refrigerator (explosion-proof)	2
Freezer	1
Ultrasonic cleaners (5 litres)	2
Laboratory glassware washing machine	1
Water distilling apparatus (8 litres/hour)	1
Water deionizing equipment (10 litres/hour)	1
Fume hoods	2
Melting-point apparatus	1
Polarimeter	1
pH meters (with assorted electrodes)	2
High-performance liquid chromatograph with variable wavelength Ultraviolet/visible detector	3 or 4

Medium-sized laboratory (cont.)	
Ultraviolet/visible spectrophotometer, double-beam	1
Infrared spectrophotometer with pellet press	1
Agate mortar with pestle	1
Gas chromatograph (flame ionization, direct and static head space injection)	1
Refractometer	1
Karl Fischer titrators (1 semi-micro and 1 coulometric for micro-determination of water)	2
Oxygen flask combustion apparatus	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution test equipment (for 6 tablets/capsules)	1
Optional items	
Atomic absorption spectrophotometer	1
Spectrofluorometer	1
High-performance liquid chromatograph detectors:	
— fluorescence	1
— diode-array	1
— refractive index	1
— evaporative light scattering (ELSD)	1
— charged aerosol (CAD)	1
— mass spectrometric (MS)	1
Gas chromatograph detectors:	
— conductivity	1
— nitrogen/phosphorous (NPD)	1
— mass spectrometric (MS)	1
Capillary electrophoresis equipment	1
Thin-layer chromatography scanner	1
Crushing strength tester	1
Friability tester	1
Viscometer	1
Ice machine	1
Solvent-recovery apparatus	1
Equipment for microbiology unit	
pH meter	1
Ultraviolet/visible spectrophotometer, single-beam	1
Microscopes (for bacteriology)	2

Medium-sized laboratory (cont.)	
Membrane filter assembly for sterility tests	1
Colony counter with magnifier	1
Laminar air flow unit	1
Hot-air sterilizer	1
Incubators, 60 litres	2 or 3
Anaerobic jar	1
Zone reader	1
Centrifuge	1
Water-bath (thermostatically controlled)	2
Autoclaves (100 litres, top-loading)	2
Refrigerators (340 litres)	2
Deep freeze	1
Laboratory glassware washing machine	1
<i>Equipment for pharmacognosy/phytochemistry unit</i>	
Grinder/mill (for preparation of sample of herbal materials)	1
Top loading balance	1
Sieves	1 set
Microscope ^b	1
Soxhlet extraction apparatus	2 or 3
Water-bath	1
Heating mantles for flasks	1 or 2
Hot plates with magnetic stirrers	2
Equipment for thin-layer chromatography	1 or 2
Developing chambers	3 or 4
Desiccators	2
Rotary vacuum apparatus	1
Distillation equipment	1
Conical percolators	2 or 3
Apparatus for determination of water content by azeotropic method ^b	1
Apparatus for determination of volatile oils ^b	1
Apparatus for determination of arsenic limit test ^c	1

^a Needed in the case that herbal medicines are also tested.

^b *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.

^c *WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues*. Geneva, World Health Organization, 2006.

Annex 2

WHO good manufacturing practices for active pharmaceutical ingredients

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 - 1.2 Regulatory applicability
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 - 5.4 Computerized systems
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 - 6.2 Equipment cleaning and use record
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 - 6.4 Master production instructions (master production and control records)
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- 6.7 Batch production record review
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References

Appendix 1

List of references for related WHO guidelines

Appendix 2

General notes: additional clarifications and explanations

This text is based on the International Conference on Harmonisation (ICH) Q7: *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*. November 2000.

1. Introduction

1.1 Objective

This document (guide) is intended to provide guidance regarding good manufacturing practices (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

In this guide “manufacturing” is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls. In this guide the term “should” indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. For the purposes of this guide, the terms “current good manufacturing practices” and “good manufacturing practices” are equivalent.

The guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This guide is not intended to define registration and filing requirements or modify pharmacopoeial requirements. This guide does not affect the ability of the responsible regulatory agency to establish specific registration or filing requirements regarding APIs within the context of marketing or manufacturing authorizations or pharmaceutical applications. All commitments in registration and filing documents must be met.

1.2 Regulatory applicability

Within the world community, materials may vary as to the legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a pharmaceutical product, it should be manufactured according to this guide.

1.3 Scope

This guide applies to the manufacture of APIs for use in finished pharmaceutical products (FPPs). It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with GMP guidelines for FPPs as defined by local authorities.

This guide covers APIs that are manufactured by chemical synthesis, extraction, cell culture or fermentation, by recovery from natural sources, or by any combination of these processes.

Specific guidance for APIs manufactured by cell culture or fermentation is described in section 18.

This guide excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this guide. In addition, the guide does not apply to medical gases, bulk-packaged FPPs, and manufacturing and control aspects specific to radiopharmaceuticals.

Section 19 contains guidance that only applies to the manufacture of APIs used in the production of FPPs specifically for clinical trials (investigational medicinal products).

An “API starting material” is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in house.

API starting materials normally have defined chemical properties and structure. The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which “API starting materials” are entered into the process. For other processes (e.g. fermentation, extraction or purification), this rationale should be established on a case-by-case basis.

Table 1 gives guidance on the point at which the API starting material is normally introduced into the process. From this point on, appropriate GMP as defined in this guide should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps shown in grey in Table 1. It does not imply that all steps shown should be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification and packaging. Physical processing of APIs, such as granulation, coating

or physical manipulation of particle size (e.g. milling and micronizing), should be conducted at least to the standards of this guide.

This GMP guide does not apply to steps prior to the introduction of the defined “API starting material”.

Table 1^a

Application of this guide to API manufacturing

Type of manufacturing	Application of this guide to steps (shown in grey) used in this type of manufacturing				
Chemical manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
“Classical” fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

^a This table has been taken from the ICH Harmonised Tripartite Guideline: Active Pharmaceutical Ingredients Q7. Current *Step 4* version, dated 10 November 2000.



2. Quality management

2.1 Principles¹

2.10 Quality should be the responsibility of all persons involved in manufacturing.

2.11 Each manufacturer should establish, document and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

2.12 The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality-related activities should be defined and documented.

2.13 There should be a quality unit(s) that is independent of production and that fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

2.14 The persons authorized to release intermediates and APIs should be specified.

2.15 All quality-related activities should be recorded at the time they are performed.

2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in section 10.20 or the use of raw materials or intermediates pending completion of evaluation).

2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g. quality related complaints, recalls and regulatory actions).

2.2 Responsibilities of the quality unit(s)

2.20 The quality unit(s) should be involved in all quality-related matters.

¹ This system of numbering sections is different to the usual WHO style. It is used here to harmonize with the guide used in inspection reports internationally.

2.21 The quality unit(s) should review and approve all appropriate quality-related documents.

2.22 The main responsibilities of the independent quality unit(s) should not be delegated.

These responsibilities should be described in writing and should include but not necessarily be limited to:

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company.
2. Establishing a system to release or reject raw materials, intermediates, packaging and labelling materials.
3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution.
4. Making sure that critical deviations are investigated and resolved.
5. Approving all specifications and master production instructions.
6. Approving all procedures impacting the quality of intermediates or APIs.
7. Making sure that internal audits (self-inspections) are performed.
8. Approving intermediate and API contract manufacturers.
9. Approving changes that potentially impact quality of intermediates or APIs.
10. Reviewing and approving validation protocols and reports.
11. Making sure that quality-related complaints are investigated and resolved.
12. Making sure that effective systems are used for maintaining and calibrating critical equipment.
13. Making sure that materials are appropriately tested and the results are reported.
14. Making sure that there are stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate.
15. Performing product quality reviews (as defined in section 2.5).

2.3 Responsibility for production activities

The responsibility for production activities should be described in writing, and should include but not necessarily be limited to:

1. Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures.
2. Producing APIs and, when appropriate, intermediates according to pre-approved instructions.
3. Reviewing all production batch records and ensuring that these are completed and signed.

4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded.
5. Making sure that production facilities are clean and when appropriate disinfected.
6. Making sure that the necessary calibrations are performed and records kept.
7. Making sure that the premises and equipment are maintained and records kept.
8. Making sure that validation protocols and reports are reviewed and approved.
9. Evaluating proposed changes in product, process or equipment.
10. Making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.4 Internal audits (self-inspection)

2.40 In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

2.41 Audit findings and corrective actions should be documented and brought to the attention of the responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

2.5 Product quality review

2.50 Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least a review of:

- critical in-process control and critical API test results;
- all batches that failed to meet established specification(s);
- all critical deviations or non-conformances and related investigations;
- any changes carried out to the processes or analytical methods;
- results of the stability monitoring programme;
- quality-related returns, complaints and recalls; and
- adequacy of corrective actions.

2.51 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

3. Personnel

3.1 Personnel qualifications

3.10 There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.

3.11 The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs, and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

3.2 Personnel hygiene

3.20 Personnel should practice good sanitation and health habits.

3.21 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.

3.22 Personnel should avoid direct contact with intermediates or APIs.

3.23 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

3.24 Personnel with an infectious disease or who have open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where their health condition could adversely affect the quality of the APIs, until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

3.3 Consultants

3.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

3.31 Records should be maintained stating the name, address, qualifications and type of service provided by these consultants.

4. Buildings and facilities

4.1 Design and construction

4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

4.12 Where the equipment itself (e.g. closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

4.14 There should be defined areas or other control systems for the following activities:

- receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;
- quarantine before release or rejection of intermediates and APIs;
- sampling of intermediates and APIs;
- holding rejected materials before further disposition (e.g. return, reprocessing or destruction);
- storage of released materials;
- production operations;
- packaging and labelling operations; and
- laboratory operations.

4.15 Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single-use towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

4.16 Laboratory areas and operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

4.2 Utilities

4.20 All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

4.21 Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

4.22 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3 Water

4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

4.31 Unless otherwise justified, process water should, at a minimum, meet WHO guidelines for drinking (potable) water quality.

4.32 If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical and chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.

4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

4.34 Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile FPP, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms and endotoxins.

4.4 Containment

4.40 Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.

4.41 Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g. certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

4.42 Appropriate measures should be established and implemented to prevent cross-contamination, e.g. from personnel or materials, moving from one dedicated area to another.

4.43 Any production activities (including weighing, milling or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.

4.5 Lighting

4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance and proper operations.

4.6 Sewage and refuse

4.60 Sewage, refuse and other waste (e.g. solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

4.7 Sanitation and maintenance

4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

4.71 Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment and materials to be used in cleaning buildings and facilities.

4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging or labelling materials, intermediates and APIs.

5. Process equipment

5.1 Design and construction

5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate) and maintenance.

5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

5.12 Production equipment should only be used within its qualified operating range.

5.13 Major equipment (e.g. reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food-grade lubricants and oils should be used.

5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

5.16 A set of current drawings should be maintained for equipment and critical installations (e.g. instrumentation and utility systems).

5.2 Equipment maintenance and cleaning

5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventive maintenance of equipment.

5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

- assignment of responsibility for cleaning of equipment;
- cleaning schedules, including, where appropriate, sanitizing schedules;
- a complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;

- when appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;
- instructions for the removal or obliteration of previous batch identification;
- instructions for the protection of clean equipment from contamination prior to use;
- inspection of equipment for cleanliness immediately before use, if practical; and
- establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

5.22 Equipment and utensils should be cleaned, stored and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, this equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of microorganisms).

5.24 Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.

5.3 Calibration

5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

5.31 Equipment calibrations should be performed using standards traceable to certified standards, if these exist.

5.32 Records of these calibrations should be maintained.

5.33 The current calibration status of critical equipment should be known and verifiable.

5.34 Instruments that do not meet calibration criteria should not be used.

5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an

impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

5.4 **Computerized systems**

5.40 GMP-related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.

5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.

5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at the time of installation, a retrospective validation could be conducted if appropriate documentation is available.

5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g the system being turned off and data not captured). There should be a record of any data change made, the previous entry, the person who made the change and when the change was made.

5.44 Written procedures should be available for the operation and maintenance of computerized systems.

5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the data entered. This can be done by a second operator or by the system itself.

5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

5.48 If system breakdowns or failures will result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.

5.49 Data can be recorded by a second means in addition to the computer system.

6. Documentation and records

6.1 Documentation system and specifications

6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.

6.11 The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.

6.12 A procedure should be established for retaining all appropriate documents (e.g. development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records and distribution records). The retention periods for these documents should be specified.

6.13 All production, control and distribution records should be retained for at least one year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least three years after the batch is completely distributed.

6.14 Entries in records should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed ensuring that the original entry remains readable.

6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities described in these records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

6.16 Specifications, instructions, procedures and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

6.17 Specifications should be established and documented for raw materials, intermediates where necessary, APIs and labelling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.

6.18 If electronic signatures are used on documents they should be authenticated and secure.

6.2 Equipment cleaning and use record

6.20 Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

6.21 If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance and use can be part of the batch record or maintained separately.

6.3 Records of raw materials, intermediates, API labelling and packaging materials

6.30 Records of raw materials, intermediates, API labelling and packaging materials should be maintained including:

- the name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for APIs; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt;
- the results of any test or examination performed and the conclusions derived from this;
- records tracing the use of materials;
- documentation of the examination and review of API labelling and packaging material for conformity with established specifications; and
- the final decision regarding rejected raw materials, intermediates or API labelling and packaging materials.

6.31 Master (approved) labels should be maintained for comparison to issued labels.

6.4 Master production instructions (master production and control records)

6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated and signed by one person and independently checked, dated and signed by a person in the quality unit(s).

6.41 Master production instructions should include:

- the name of the intermediate or API being manufactured and an identifying document reference code, if applicable;

- a complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;
- an accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified;
- the production location and major production equipment to be used;
- detailed production instructions, including the:
 - sequences to be followed,
 - ranges of process parameters to be used,
 - sampling instructions and in-process controls with their acceptance criteria, where appropriate,
 - time limits for completion of individual processing steps and/or the total process, where appropriate, and
 - expected yield ranges at appropriate phases of processing or time;
- where appropriate, special notations and precautions to be followed, or cross-references to these; and
- the instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

6.5 **Batch production records (batch production and control records)**

6.50 Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and is a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

6.51 These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code, together with the date and time, can serve as the unique identifier until the final number is allocated.

6.52 Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

- dates and, when appropriate, times;
- identity of major equipment (e.g., reactors, driers and mills) used;

- specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;
- actual results recorded for critical process parameters;
- any sampling performed;
- signatures of the persons performing and directly supervising or checking each critical step in the operation;
- in-process and laboratory test results;
- actual yield at appropriate phases or times;
- description of packaging and label for intermediate or API;
- representative label of API or intermediate if made commercially available;
- any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately; and
- results of release testing.

6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

6.6 Laboratory control records

6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- a description of samples received for testing, including the name of the material or its source, batch number or other distinctive code, the date the sample was taken and, where appropriate, the quantity and date the sample was received for testing;
- a statement of or reference to each test method used;
- a statement of the weight or measure of sample used for each test as described by the method;
- data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions;
- a complete record of all raw data generated during each test, in addition to graphs, charts and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested;
- a record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors and equivalency factors;
- a statement of the test results and how they compare with established acceptance criteria;

- the signature of the person who performed each test and the date(s) the tests were performed; and
- the date and signature of a second person showing that the original records have been reviewed for accuracy, completeness and compliance with established standards.

6.61 Complete records should also be maintained for:

- any modifications to an established analytical method;
- periodic calibration of laboratory instruments, apparatus, gauges and recording devices;
- all stability testing performed on APIs; and
- out-of-specification (OOS) investigations.

6.7 Batch production record review

6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labelling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

6.72 All deviation, investigation and OOS reports should be reviewed as part of the batch record review before the batch is released.

6.73 The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

7. Materials management

7.1 General controls

7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials.

7.11 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).

7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known to the intermediate and/or API manufacturer.

7.14 Changing the source of supply of critical raw materials should be done according to section 13, Change control.

7.2 Receipt and quarantine

7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), damage to containers, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and then released for use.

7.21 Before incoming materials are mixed with existing stocks (e.g. solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

7.22 If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

- certificate of cleaning;
- testing for trace impurities;
- audit of the supplier.

7.23 Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.

7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

7.3 Sampling and testing of incoming production materials

7.30 At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in section 7.32. A supplier's certificate of analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g. past quality history) that the manufacturer can consistently

provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the certificates of analysis. Reliability of certificates of analysis should be checked at regular intervals.

7.32 Processing aids, hazardous or highly toxic raw materials, other special materials or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's certificate of analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The decision on the number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, variability of the material, past quality history of the supplier and the quantity needed for analysis.

7.34 Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

7.35 Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

7.4 Storage

7.40 Materials should be handled and stored in such a manner as to prevent degradation, contamination and cross-contamination.

7.41 Materials stored in fibre drums, bags or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

7.42 Materials should be stored under conditions and for a period that will have no adverse affect on their quality and should normally be controlled so that the oldest stock is used first.

7.43 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

7.5 Re-evaluation

7.50 Materials should be re-evaluated as appropriate to determine their suitability for use (e.g. after prolonged storage or exposure to heat or humidity).

8. Production and in-process controls

8.1 Production operations

8.10 Raw materials for manufacturing of intermediates and APIs should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

- material name and/or item code;
- receiving or control number;
- weight or measure of material in the new container; and
- re-evaluation or retest date if appropriate.

8.12 Critical weighing, measuring or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

8.13 Other critical activities should be witnessed or subjected to an equivalent control.

8.14 Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.

8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems or alternative means.

8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

8.2 Time limits

8.20 If time limits are specified in the master production instruction (see section 6.41), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g. pH adjustment, hydrogenation or drying to a predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

8.3 In-process sampling and controls

8.30 Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.

8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g. isolation and purification steps).

8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).

8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s)' approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

8.34 Written procedures should describe the sampling methods for in-process materials, intermediates and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

8.35 In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or

APIs. Procedures should be established to ensure the integrity of samples after collection.

8.36 OOS investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

8.4 **Blending batches of intermediates or APIs**

8.40 For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g. collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

8.41 OOS batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

8.42 Acceptable blending operations include but are not limited to:

- blending of small batches to increase batch size;
- blending of tailings (i.e. relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.

8.43 Blending processes should be adequately controlled and documented and the blended batch should be tested for conformance to established specifications where appropriate.

8.44 The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

8.45 Where physical attributes of the API are critical (e.g. APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g. particle size distribution, bulk density and tap density) that may be affected by the blending process.

8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

8.47 The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

8.5 Contamination control

8.50 Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carry-over should not result in the carry-over of degradants or microbial contamination that may adversely alter the established impurity profile of the API.

8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

8.52 Precautions to avoid contamination should be taken when APIs are handled after purification.

9. Packaging and identification labelling of APIs and intermediates

9.1 General

9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release and handling of packaging and labelling materials.

9.11 Packaging and labelling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

9.12 Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing and whether they are accepted or rejected.

9.2 Packaging materials

9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive or absorptive to ensure that they do not alter the quality of the intermediate or API beyond the specified limits.

9.22 If containers are reused, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

9.3 Label issuance and control

9.30 Access to the label storage areas should be limited to authorized personnel.

9.31 Procedures should be used to reconcile the quantities of labels issued, used and returned and to evaluate discrepancies found between the number of containers labelled and the number of labels issued. Such discrepancies should be investigated and the investigation should be approved by the quality unit(s).

9.32 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be retained and stored in a manner that prevents mix-ups and provides proper identification.

9.33 Obsolete and outdated labels should be destroyed.

9.34 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

9.35 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

9.36 A printed label representative of those used should be included in the batch production record.

9.4 Packaging and labelling operations

9.40 There should be documented procedures designed to ensure that the correct packaging materials and labels are used.

9.41 Labelling operations should be designed to prevent mix-ups. They should be physically or spatially separated from operations involving other intermediates or APIs.

9.42 Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product and the storage conditions, when such information is critical to assure the quality of the intermediate or API.

9.43 If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, this date should be indicated on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

9.44 Packaging and labelling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log or other documentation system.

9.45 Packaged and labelled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

9.46 Intermediate or API containers that are transported outside the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

10. Storage and distribution

10.1 Warehousing procedures

10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

10.11 Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

10.2 Distribution procedures

10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality.

10.22 Special transport or storage conditions for an API or intermediate should be stated on the label.

10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

10.24 A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

11. Laboratory controls

11.1 General controls

11.10 The independent quality unit(s) should have at its disposal adequate laboratory facilities.

11.11 There should be documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data. Laboratory records should be maintained in accordance with section 6.6.

11.12 All specifications, sampling plans and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and be consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

11.14 Laboratory controls should be followed and documented at the time of performance. Any departures from the above-described procedures should be documented and explained.

11.15 Any OOS result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.

11.16 Reagents and standard solutions should be prepared and labelled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.

11.17 Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

11.18 Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

11.19 Secondary reference standards should be appropriately prepared, identified, tested, approved and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

11.2 Testing of intermediates and APIs

11.20 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

11.21 An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed and classification of each identified impurity (e.g. inorganic, organic or solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs of herbal or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B (1).

11.22 The impurity profile should be compared at appropriate intervals with the impurity profile in the regulatory submission or compared with historical data in order to detect changes to the API resulting from modifications to raw materials, equipment operating parameters or the production process.

11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

11.3 Validation of analytical procedures

See section 12.

11.4 Certificates of analysis

11.40 Authentic certificates of analysis should be issued for each batch of intermediate or API on request.

11.41 Information on the name of the intermediate or API, including where appropriate its grade, the batch number and the date of release, should be provided on the certificate of analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

11.42 The certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits and the numerical results obtained (if test results are numerical).

11.43 Certificates should be dated and signed by authorized personnel from the quality unit(s) and should show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reproprocessor, the certificate of analysis should show the name, address and telephone number of the repacker or reproprocessor and a reference to the name of the original manufacturer.

11.44 If new certificates are issued by or on behalf of repackers or reproprocessors, agents or brokers, these certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch certificate, a copy of which should be attached.

11.5 Stability monitoring of APIs

11.50 A documented, ongoing testing programme should be designed to monitor the stability characteristics of APIs and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

11.51 The test procedures used in stability testing should be validated and be stability-indicating.

11.52 Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fibre drums, stability samples can be packaged in bags of the same material and in smaller drums of similar or identical material composition to the drums in which the API is marketed.

11.53 Normally the first three commercial production batches should be placed on the stability monitoring programme to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.

11.54 Thereafter at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring programme and tested at least annually to confirm the stability.

11.55 For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biological and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first three months, and at three-monthly intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g. nine-month testing) can be considered.

11.56 Where appropriate, the stability storage conditions should be consistent with the WHO guidelines on stability.

11.6 Expiry and retest dating

11.60 When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data and test results).

11.61 An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

11.62 Preliminary API expiry or retest dates can be based on pilot-scale batches if:

- the pilot batches employ a method of manufacture and a procedure that simulates the final process to be used on a commercial manufacturing scale; and
- the quality of the API represents the material to be made on a commercial scale.

11.63 A representative sample should be taken for the purpose of performing a retest.

11.7 Reserve/retention samples

11.70 The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing.

11.71 Appropriately identified reserve samples of each batch of API should be retained for one year after the expiry date assigned by the manufacturer to the batch, or for three years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for three years after the batch has been completely distributed by the manufacturer.

11.72 The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

12. Validation

12.1 Validation policy

12.10 The company's overall policy, intentions and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems and personnel responsible for design, review, approval and documentation of each validation phase, should be documented.

12.11 The critical parameters and attributes should normally be identified during the development stage or from historical data and the ranges necessary for the reproducible operation should be defined. This should include:

- defining the API in terms of its critical product attributes;
- identifying process parameters that could affect the critical quality attributes of the API;
- determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

12.12 Validation should extend to those operations determined to be critical to the quality and purity of the API.

12.2 Validation documentation

12.20 A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

12.21 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective or concurrent) and the number of process runs.

12.22 A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

12.23 Any variations from the validation protocol should be documented with appropriate justification.

12.3 Qualification

12.30 Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- design qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose;
- installation qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements;
- operational qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges;
- performance qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4 Approaches to process validation

12.40 Process validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

12.41 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These three approaches and their applicability are outlined below.

12.42 Prospective validation should normally be performed for all API processes as defined in section 12.1.3. Prospective validation performed on an API process should be completed before the commercial distribution of the FPP manufactured from that API.

12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API

batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in FPPs for commercial distribution based on thorough monitoring and testing of the API batches.

12.44 An exception can be made for retrospective validation for well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities or the production process. This validation approach may be used where:

- (1) Critical quality attributes and critical process parameters have been identified.
- (2) Appropriate in-process acceptance criteria and controls have been established.
- (3) There have not been significant process or product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability.
- (4) Impurity profiles have been established for the existing API.

12.45 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

12.5 Process validation programme

12.50 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g. complex API processes or API processes with prolonged completion times). Generally, for retrospective validation, data from 10 to 30 consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

12.52 Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined

during process development or for batches used for pivotal clinical and toxicological studies.

12.6 Periodic review of validated systems

12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

12.7 Cleaning validation

12.70 Cleaning procedures should normally be validated. In general cleaning validation should be directed to those situations or process steps where contamination or carry-over of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity and stability.

12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labelled.

12.73 Sampling should include swabbing, rinsing or alternative methods (e.g. direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g. inner surfaces of hoses, transfer pipes, reactor tanks with small ports for handling toxic materials and small intricate equipment such as micronizers and microfluidizers).

12.74 Validated analytical methods with the sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable

level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable and verifiable and be based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological or physiological activity of the API or its most deleterious component.

12.75 Equipment cleaning or sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g. non-sterile APIs used to manufacture sterile products).

12.76 Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise remain undetected by sampling and/or analysis.

12.8 Validation of analytical methods

12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

12.81 Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.

12.83 Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

13. Change control

13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.

13.11 Written procedures should cover the identification, documentation, appropriate review, and approval of changes in raw materials, specifications,

analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software.

13.12 Any proposals for relevant changes to GMP should be drafted, reviewed and approved by the appropriate organizational units and reviewed and approved by the quality unit(s).

13.13 The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on their nature and extent and the effects these changes may have on the process. Scientific judgement should be used to determine what additional testing and validation studies are appropriate to justify a change in a validated process.

13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

13.15 After the change has been implemented there should be an evaluation of the first batches produced or tested under the change.

13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability programme and/or can be added to the stability monitoring programme.

13.17 Manufacturers of the current dosage form should be notified of changes from established production and process control procedures that can impact the quality of the API.

14. Rejection and reuse of materials

14.1 Rejection

14.10 Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

14.2 Reprocessing

14.20 Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g. distillation, filtration,

chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches it should be included as part of the standard manufacturing process.

14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

14.22 Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely affected due to the potential formation of by-products and overreacted materials.

14.3 Reworking

14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.

14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.

14.32 Procedures should provide for comparing the impurity profile of each reworked batch with batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

14.4 Recovery of materials and solvents

14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or comingling with other approved materials.

14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

14.43 The use of recovered solvents, mother liquors and other recovered materials should be adequately documented.

14.5 Returns

14.50 Returned intermediates or APIs should be identified as such and quarantined.

14.51 If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return, or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked or destroyed, as appropriate.

14.52 Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

- name and address of the consignee;
- intermediate or API, batch number and quantity returned;
- reason for return; and
- use or disposal of the returned intermediate or API.

15. Complaints and recalls

15.10 All quality-related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

15.11 Complaint records should include:

- name and address of complainant;
- name (and, where appropriate, title) and telephone number of person submitting the complaint;
- nature of the complaint (including name and batch number of the API);
- date the complaint was received;
- action initially taken (including dates and identity of person taking the action);
- any follow-up action taken;
- response provided to the originator of complaint (including date on which the response was sent); and
- final decision on intermediate or API batch or lot.

15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies and severity with a view to taking additional, and if appropriate, immediate corrective action.

15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall and how the recalled material should be treated.

15.15 In the event of a serious or potentially life-threatening situation, local, national and/or international authorities should be informed and their advice sought.

16. Contract manufacturers (including laboratories)

16.10 All contract manufacturers (including laboratories) should comply with GMP defined in this guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

16.11 Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations taking place at the contract sites.

16.12 There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.

16.13 The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.

16.14 Where subcontracting is allowed the contract acceptor should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements.

16.15 Manufacturing and laboratory records should be kept at the site where the activity takes place and be readily available.

16.16 Changes in the process, equipment, test methods, specifications or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

17. Agents, brokers, traders, distributors, repackers and relabellers

17.1 Applicability

17.10 This section applies to any party other than the original manufacturer who may trade and/or take possession of, repack, relabel, manipulate, distribute or store an API or intermediate.

17.11 All agents, brokers, traders, distributors, repackers and relabellers should comply with GMP as defined in this guide.

17.2 Traceability of distributed APIs and intermediates

17.20 Agents, brokers, traders, distributors, repackers or relabellers should maintain complete traceability of the APIs and intermediates that they distribute. Documents that should be retained and available should include:

- identity of original manufacturer;
- address of original manufacturer;
- purchase orders;
- bills of lading (transportation documentation);
- receipt documents;
- name or designation of API or intermediate;
- manufacturer's batch number;
- transportation and distribution records;
- all authentic certificates of analysis, including those of the original manufacturer; and
- retest or expiry date.

17.3 Quality management

17.30 Agents, brokers, traders, distributors, repackers or relabellers should establish, document and implement an effective system of managing quality, as specified in section 2.

17.4 Repackaging, relabelling and holding of APIs and intermediates

17.40 Repackaging, relabelling and holding of APIs and intermediates should be performed under appropriate GMP controls as stipulated in this guide, to avoid mix-ups and loss of API or intermediate identity or purity.

17.41 Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

17.5 Stability

17.50 Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the manufacturer of the API or intermediate.

17.6 Transfer of information

17.60 Agents, brokers, distributors, repackers or relabellers should transfer all quality or regulatory information received from the manufacturer

of an API or intermediate to the customer, and from the customer to the manufacturer of the API or intermediate.

17.61 The agent, broker, trader, distributor, repacker or relabeller who supplies the API or intermediate to the customer should provide the name of the original manufacturer of the API or intermediate and the batch number(s) supplied.

17.62 The agent should also provide the identity of the manufacturer of the original API or intermediate to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original manufacturer of the API or intermediate. (In this context “authorized” refers to authorized by the manufacturer.)

17.63 The specific guidance for certificates of analysis included in section 11.4 should be met.

17.7 Handling of complaints and recalls

17.70 Agents, brokers, traders, distributors, repackers or relabellers should maintain records of complaints and recalls as specified in section 15 for all complaints and recalls that come to their attention.

17.71 If the situation warrants, the agents, brokers, traders, distributors, repackers or relabellers should review the complaint with the manufacturer of the original API or intermediate to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

17.72 Where a complaint is referred to the original manufacturer of the API or intermediate, the record maintained by the agents, brokers, traders, distributors, repackers or relabellers should include any response received from the original manufacturer of the API or intermediate (including date and information provided).

17.8 Handling of returns

17.80 Returns should be handled as specified in section 14.5.3. The agents, brokers, traders, distributors, repackers or relabellers should maintain documentation of returned APIs and intermediates.

18. **Specific guidance for APIs manufactured by cell culture/fermentation²**

18.1 **General**

18.10 Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for “classical” processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

18.11 The term “biotechnological process” (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

18.12 The term “classical fermentation” refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g. irradiation or chemical mutagenesis) to produce APIs. APIs produced by “classical fermentation” are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

18.13 Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral

² This section has been referred to the Expert Committee on Biological Standardization for discussion and consideration. Reproduced here but currently not adopted by the aforementioned Expert Committee.

contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

18.14 Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this guide starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

18.15 Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed or contained systems).

18.16 In general, process controls should take into account:

- maintenance of the working cell bank (where appropriate);
- proper inoculation and expansion of the culture;
- control of the critical operating parameters during fermentation/cell culture;
- monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;
- harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;
- monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and
- viral safety concerns as described in ICH Guideline Q5A (2)..

18.17 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

18.2 Cell bank maintenance and record keeping

18.20 Access to cell banks should be limited to authorized personnel.

18.21 Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

18.22 Records of the use of the vials from the cell banks and storage conditions should be maintained.

18.23 Where appropriate, cell banks should be periodically monitored to determine suitability for use.

18.24 See ICH Guideline Q5D (3) for a more complete discussion of cell banking.

18.3 Cell culture/fermentation

18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

18.31 Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

18.32 Personnel should be appropriately gowned and take special precautions handling the cultures.

18.33 Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.

18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.

18.36 There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

18.37 Records of contamination events should be maintained.

18.38 Shared (multiproduct) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

18.4 Harvesting, isolation and purification

18.40 Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.

18.41 Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.

18.42 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

18.43 If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

18.44 Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

18.5 Viral removal/inactivation steps

18.50 See the ICH Guideline Q5A (2) for more specific information.

18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.

18.52 Appropriate precautions should be taken to prevent potential viral contamination from pre-viral to post-viral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.

18.53 The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g. through equipment or environment) from previous steps.

19. APIs for use in clinical trials

19.1 General

19.10 Not all the controls in the previous sections of this guide are appropriate for the manufacture of a new API for investigational use during

its development. Section 19 provides specific guidance unique to these circumstances.

19.11 The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the pharmaceutical product incorporating the API. Process and test procedures should be flexible to allow for changes to be made as knowledge of the process increases and clinical testing of a pharmaceutical product progresses from the preclinical stages through the clinical stages. Once pharmaceutical development reaches the stage where the API is produced for use in pharmaceutical products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

19.2 Quality

19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism for the approval of each batch.

19.21 A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

19.22 Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

19.23 Quality measures should include a system for testing of raw materials, packaging materials, intermediates and APIs.

19.24 Process and quality problems should be evaluated.

19.25 Labelling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

19.3 Equipment and facilities

19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.

19.31 Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

19.4 Control of raw materials

19.40 Raw materials used in production of APIs for use in clinical trials should be evaluated by testing or be received with a supplier's analysis and

subjected to identity testing. When a material is considered hazardous a supplier's analysis should suffice.

19.41 In some instances the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e. use testing) rather than on analytical testing alone.

19.5 Production

19.50 The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records or by other appropriate means. These documents should include information on the use of production materials, equipment, processing and scientific observations.

19.51 Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

19.6 Validation

19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate where a single API batch is produced or where process changes during development of an API make batch replication difficult or inexact. The combination of controls, calibration and, where appropriate, equipment qualification assures quality of the API during this development phase.

19.61 Process validation should be conducted in accordance with section 12 when batches are produced for commercial use, even when such batches are produced on a pilot scale or small scale.

19.7 Changes

19.70 Changes are expected during development as knowledge is gained and the production is scaled up. Every change in the production, specifications or test procedures should be adequately recorded.

19.8 Laboratory controls

19.80 While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated they should be scientifically sound.

19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination or discontinuation of an application.

19.82 Expiry and retest dating as defined in section 11.6 applies to existing APIs used in clinical trials. For new APIs section 11.6 does not normally apply in early stages of clinical trials.

19.9 Documentation

19.90 A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

19.91 The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

19.92 A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination or discontinuation of an application.

20. Glossary

acceptance criteria

Numerical limits, ranges or other suitable measures for acceptance of test results.

active pharmaceutical ingredient (API) (or pharmaceutical substance)

Any substance or mixture of substances intended to be used in the manufacture of a finished pharmaceutical product (FPP) and that, when used in the production of a pharmaceutical product, becomes an active ingredient of the pharmaceutical product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

API starting material

A raw material, intermediate or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house. API starting materials normally have defined chemical properties and structure.

batch (or lot)

A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case

of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

batch number (or lot number)

A unique combination of numbers, letters and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

bioburden

The level and type (e.g. objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

calibration

The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

computer system

A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

computerized system

A process or operation integrated with a computer system.

contamination

The undesired introduction of impurities of a chemical or microbiological nature or of foreign matter into or on to a raw material, intermediate or API during production, sampling, packaging or repackaging, storage or transport.

contract manufacturer

A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

critical

Describes a process step, process condition, test requirement or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

cross-contamination

Contamination of a material or product with another material or product.

deviation

Departure from an approved instruction or established standard.

expiry date (or expiration date)

The date placed on the container or labels of an API designating the time during which the API is expected to remain within established shelf-life specifications if stored under defined conditions and after which it should not be used.

finished pharmaceutical product (FPP)

ICH: The dosage form in the final immediate packaging intended for marketing (reference Q1A (4)).

WHO: A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more APIs.

impurity

Any component present in the intermediate or API that is not the desired entity.

impurity profile

A description of the identified and unidentified impurities present in an API.

in-process control (or process control)

Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

intermediate

A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated.

(Note: this guide only addresses those intermediates produced after the point that the company has defined as the point at which the production of the API begins.)

lot

See Batch.

lot number

See Batch number.

manufacture

All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and related controls.

material

A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labelling materials.

mother liquor

The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API and/or impurities. It may be used for further processing.

packaging material

Any material intended to protect an intermediate or API during storage and transport.

pharmaceutical substance

See Active pharmaceutical ingredient.

procedure

A documented description of the operations to be performed, the precautions to be taken and measures to be applied, directly or indirectly related to the manufacture of an intermediate or API.

process aids

Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid or activated carbon).

process control

See In-process control.

production

All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

qualification

Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

quality assurance (QA)

The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

quality control (QC)

Checking or testing that specifications are met.

quality unit(s)

An organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

quarantine

The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

raw material

A general term used to denote starting materials, reagents and solvents intended for use in the production of intermediates or APIs.

reference standard, primary

A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be:

- obtained from an officially recognized source;
- prepared by independent synthesis;
- obtained from existing production material of high purity; or
- prepared by further purification of existing production material.

reference standard, secondary

A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

reprocessing

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g. distillation, filtration, chromatography or milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process and not to be reprocessing.

retest date

The date when a material should be re-examined to ensure that it is still suitable for use.

reworking

Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g. recrystallizing with a different solvent).

signature (signed)

See Signed.

signed (signature)

The record of the individual who performed a particular action or review. This record can be in the form of initials, full handwritten signature, personal seal or an authenticated and secure electronic signature.

solvent

An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

specification

A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

validation

A documented programme that provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting predetermined acceptance criteria.

validation protocol

A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters and operating ranges, product characteristics, sampling, test data to be collected, number of validation runs and acceptable test results.

yield, expected

The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot-scale or manufacturing data.

yield, theoretical

The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

References

1. *ICH Harmonised Tripartite Guideline: Specifications: test procedures and acceptance criteria for biotechnological/biological products Q6B*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999.
2. *ICH Harmonised Tripartite Guideline: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin Q5A*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999.
3. *ICH Harmonised Tripartite Guideline: Derivation and characterisation of cell substrates used for production of biotechnological/biological products Q5D*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1997.
4. *ICH Harmonised Tripartite Guideline: Stability testing of new drug substances and products Q1A*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2003.

Appendix 1

List of references for related WHO guidelines

Distribution

(http://www.who.int/medicines/areas/quality_safety/quality_assurance/distribution/en/)

Good trade and distribution practices for pharmaceutical starting materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2003, Annex 2 (WHO Technical Report Series, No. 917).

WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2003, Annex 3 (WHO Technical Report Series, No. 917).

Guide to good storage practices for pharmaceuticals In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003, Annex 9 (WHO Technical Report Series, No. 908).

Production

(http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html)

Good Manufacturing Practices for Pharmaceutical Products: Main Principles. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003, Annex 4 (WHO Technical Report Series, No. 908).

Good manufacturing practices: requirement for the sampling of starting materials (amendment). In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005, Annex 2 (WHO Technical Report Series, No. 929).

Sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 6 (WHO Technical Report Series, No. 902).

Investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*.

Thirty-fourth report. Geneva, World Health Organization, 1996, Annex 7 (WHO Technical Report Series, No. 863).

Herbal medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World Health Organization, 2006, Annex 3 (WHO Technical Report Series, No. 937).

Water for pharmaceutical use. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report.* Geneva, World Health Organization, 2005, Annex 3 (WHO Technical Report Series, No. 929).

Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World Health Organization, 2006, Annex 2 (WHO Technical Report Series, No. 937).

Validation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World Health Organization, 2006, Annex 4 (WHO Technical Report Series, No. 937).

Quality control

(http://www.who.int/medicines/areas/quality_safety/quality_assurance/control/en/index.html)

The International Pharmacopoeia (Ph. Int.) — Fourth Edition + First Supplement. Geneva, World Health Organization, 2006.

General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report.* Geneva, World Health Organization, 2007, Annex 3 (WHO Technical Report Series, No. 943).

Considerations for requesting analyses of drug samples. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002, Annex 4 (WHO Technical Report Series, No. 902).

Model certificate of analysis. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002, Annex 10 (WHO Technical Report Series, No. 902).

Related regulatory standards

(http://www.who.int/medicines/areas/quality_safety/quality_assurance/regulatory_standards/en/)

Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 2 (WHO Technical Report Series, No. 953).

Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 4 (WHO Technical Report Series, No. 953).

Guidelines on active pharmaceutical ingredient master file procedure. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-second report*. Geneva, World Health Organization, 2008, Annex 4 (WHO Technical Report Series, No. 948).

Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007, Annex 6 (WHO Technical Report Series, No. 943).

WHO guidelines for sampling of pharmaceutical products and related materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005, Annex 4 (WHO Technical Report Series, No. 929).

Appendix 2

General notes: additional clarifications and explanations

2.1.1 The intent of this clause is that senior management of the API manufacturer has the responsibility to ensure that there is an effective quality management system in place and that all employees are made aware of their roles and responsibilities in assuring the quality of the API(s) produced.

2.3 The intent of this clause is to specify the roles and responsibilities that should apply to production activities and, in particular, that these responsibilities should not be delegated to non-production personnel within the company or to any persons outside the company.

5.2.1 This clause requires a written standard operating procedure (SOP) covering the maintenance of equipment. Important information to specify in this SOP should include:

- who is responsible for coordinating equipment maintenance activities (usually production management or engineering management);
- a provision that a schedule of planned preventive maintenance of equipment should be available (a useful reference is *ISPE Good Practice Guide: Maintenance*, May 2009) (1);
- a statement of the necessity to follow proper change control procedures where non-routine repairs, or modifications, replacements or other activities, are required.

7.1.2 There is an expectation that suppliers of critical materials should be subject to on-site audits as part of the company's supplier qualification programme.

7.2.1 There is an expectation that upon receipt and before acceptance of materials, each container or grouping of containers of materials should be examined visually for correct labelling, including correlation between the name used by the supplier and the in-house name. If these names are different, both names should be recorded and verified against a previously approved list of synonyms and checked by a scientifically qualified person.

7.3.1 This clause requires that at least one test be performed to verify the identity of each batch of material received. For clarification, one test for identity may not be sufficient in the majority of cases as this is dependent on various aspects, including supplier qualification.

11.7.3 For clarification, the reserve sample should be stored in a packaging system designed to give maximum protection of the API against change over time, e.g. a glass bottle with tightly fitted cap.

17. Refer to WHO GTDP (2) and WHO GMP for excipients (3).
18. See footnote on p. 174.

API starting material

As discussed in this document the introduction of the API starting material into the manufacturing process is where the requirements of GMP commence.

The API starting material itself needs to be proposed and justified by the manufacturer and accepted as such by assessors. This justification should be documented and be available for review by WHO GMP inspectors.

The API starting material should be fully characterized according to identity and purity. In addition, the steps prior to the step where the API starting material appears, which may involve “starting materials for synthesis”, should be available in the form of a flow chart.

In general, the starting materials for synthesis should:

- be a synthetic precursor one or more synthetic steps prior to the final API intermediate;
- be a well characterized, isolated and purified substance with a fully elucidated structure;
- have well defined specifications which include one or more specific identity tests, and tests and limits for potency, specified and unspecified impurities and total impurities.

References

1. International Society for Pharmaceutical Engineering. *ISPE good practice guide: maintenance*. 2009 (http://www.ispe.org/cs/ispe_good_practice_guides_section/ispe_good_practice_guides).
2. Good trade and distribution practices for pharmaceutical starting materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2003, Annex 2 (WHO Technical Report Series, No. 917) (http://www.who.int/medicines/areas/quality_safety/quality_assurance/distribution/en/index.html).
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Annex 3

WHO good manufacturing practices for pharmaceutical products containing hazardous substances

1. Introduction
2. General
3. Glossary
4. Risk assessment
5. Product protection
6. Personal protection equipment and breathing air systems
7. Environmental protection
8. Facility layout
9. Air-handling systems
10. Air-handling units
11. Safe change filter housings
12. Personnel decontamination systems
13. Effluent treatment
14. Maintenance
15. Qualification and validation

References

1. Introduction

1.1 These guidelines set out good practices applicable to facilities handling pharmaceutical products (including active pharmaceutical ingredients (APIs)) that contain hazardous substances such as certain hormones, steroids or cytotoxins. They do not replace national legislation for protection of the environment and personnel. Other WHO guides to good manufacturing practices (GMP) and regulations need to be observed in addition to the workers' safety criteria (1–4).

1.2 These guidelines are to be read in conjunction with other WHO GMP guidelines with respect to building finishes and general services installations, among others. See the reference list for relevant publications which serve as additional background material. The primary focus of these guidelines is on the air-conditioning and ventilation systems of the facility; however, the document also provides some guidance on personnel protection.

1.3 The areas to which this document applies include all zones where the handling of products could lead to cross-contamination, exposure of personnel, or discharge to the environment. This includes research and development facilities, and the sites of API manufacturing and storage and of finished product manufacturing.

1.4 Where possible products should be manufactured in closed systems.

2. General

2.1 Facilities should be designed and operated in accordance with the main GMP principles, as follows:

- to ensure quality of product;
- to protect the operators from possible harmful effects of products containing hazardous substances; and
- to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.

2.2 The production of certain products containing hazardous substances should generally be conducted in separate, dedicated, self-contained facilities.

These *self-contained facilities* may be in the same building as another facility but should be separated by a physical barrier and have, e.g. separate entrances, staff facilities and air-handling systems. The extent of the separation from adjacent facilities and sharing of common services should be determined by risk assessment.

2.3 In general these manufacturing facilities should be regarded as containment facilities.

2.4 The effective operation of a facility may require the combination of some or all of the following aspects:

- appropriate facility design and layout, with the emphasis on safely containing the materials being handled. Manufacturing processes using closed systems or barrier technology enhance operator and product protection;
- manufacturing process controls including adherence to standard operating procedures (SOPs);
- appropriately designed environmental control systems (ECS) or heating, ventilation and air-conditioning (HVAC);
- extraction systems;
- personal protective equipment (PPE);
- appropriate degowning and decontamination procedures;
- industrial hygiene (monitoring staff exposure levels);
- medical surveillance (monitoring staff exposure levels); and
- administrative controls.

3. **Glossary**

The definitions given below apply to terms used in these guidelines. They may have a different meaning in other contexts.

action limit

The action limit is reached when the acceptance criteria of a critical parameter have been exceeded. Results outside these limits will require specified action and investigation.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

air-handling unit (AHU)

The air-handling unit serves to condition the air and provide the required air movement within a facility.

airlock

An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of

controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods (this can be a personnel airlock (PAL) or a material airlock (MAL)).

alert limit

The alert limit is reached when the normal operating range of a critical parameter has been exceeded, indicating that corrective measures may need to be taken to prevent the action limit being reached.

barrier technology

A system designed to segregate people from the product, contain contaminants or segregate two areas, which could be a barrier isolator (BI) or a restricted access barrier system (RABS):

- A BI is a unit supplied with high-efficiency particulate air (HEPA) filtered air that provides uncompromised continuous isolation of its interior from the external environment, including surrounding clean room air and personnel.
- A RABS is a type of barrier system that reduces or eliminates interventions into the critical zone. In practice, its level of contamination control is less than that of a barrier isolator.

clean room

A room or area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

commissioning

Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at the conclusion of project construction but prior to validation.

containment

A process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

contamination

The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.

cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or material during production.

design condition

Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

environmental control system (ECS)

Environmental control system, also referred to as heating, ventilation and air-conditioning (HVAC).

facility

The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

hazardous substance or product

A product or substance that may present a substantial risk of injury, to health or to the environment.

heating, ventilation and air-conditioning (HVAC)

Heating, ventilation and air-conditioning, also referred to as environmental control system (ECS).

high efficiency particulate air (HEPA) filter

High efficiency particulate air filter.

ISO 14644

International standard relating to the design, classification and testing of clean environments (5).

laminar airflow (LAF)

A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow).

normal operating range

The range that the manufacturer selects as the acceptable values for a parameter during normal operations. This range must be within the operating range.

occupational exposure level (OEL)

Airborne concentration of substances that will not result in adverse effects to most healthy workers, exposed for 8 hours/day, 40 hours/week.

operating range

The range of validated critical parameters within which acceptable products can be manufactured.

personal protective equipment (PPE)

The necessary garments and equipment required to protect the operator in the workplace.

pressure cascade

A process whereby air flows from one area, which is maintained at a higher pressure, to another area at a lower pressure.

qualification

The planning, carrying out and recording of tests on equipment and a system, which forms part of the validated process, to demonstrate that it will perform as intended.

standard operating procedure (SOP)

An authorized written procedure, giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (e.g. operation of equipment, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

unidirectional airflow (UDAF)

A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines.

validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

4. **Risk assessment**

4.1 Not all products containing hazardous substances are equally potent and risk assessments should be carried out to determine the potential hazards to operators and to the environment. The risk assessment should also determine which phases of the product production and control cycles, from manufacture of the API to distribution of the finished product, would fall under the requirements of these guidelines. Risk assessments applicable to the environment should include airborne contamination as well as liquid effluent contamination.

4.2 Assuming that the risk assessment determines that the products or materials being handled pose a risk to the operators and/or the public and/or the environment, the guidelines to be followed for the design and operation of the facility should be as detailed in this document.

4.3 The toxicological data available, such as permissible occupational exposure levels (OEL) for the product, should be taken into account when conducting the risk assessment.

4.4 The risk assessment should take into account the national or international occupational health and safety requirements for OELs in the work environment.

5. **Product protection**

5.1 The requirement for producing quality products, with respect to protection from contamination and cross-contamination, clean room class of air, temperature and humidity should be as for other pharmaceutical products. These requirements are covered in other WHO GMP guidelines.

6. **Personal protection equipment and breathing air systems**

6.1 The fundamental design principle for a facility and its production equipment is to provide product containment and operator protection. Should the facility and equipment design not provide adequate product containment, operator protection should be provided. If facility and equipment design are adequate, a spillage or non-routine incident could cause a hazardous situation, in which case PPE should be available. Unless otherwise specified in the material safety data sheet, operators should be protected from exposure with an appropriate method, such as by wearing:

- flash-spun, high-density polyethylene fibre material suits or impervious washable protective suits. Integral hoods may be required depending on the respirator type used;
- flash-spun, high-density polyethylene fibre material shoes, lower leg covers or cleanable boots;
- suitable single-use, disposable gloves. Double gloves should be worn where direct active contact with the product cannot be avoided. Gloves should be taped or sealed on to the protective suit sleeves; and
- respirator eye and face protection with associated breathing air systems.

6.2 Where breathing air systems are used, these should be provided to supply safe breathing air to the operators to prevent them from inhaling air from within the facility. Personnel should be appropriately trained and assessed in the use of these systems before they can enter the area. The breathing air systems should comprise a protective face mask, which should form an integral part of a protective suit. The breathing air systems could be any of the systems described below:

- a central air supply system which connects to the operator's face mask by means of flexible hoses and quick coupling sockets, also called an airline respirator (AR). The air connection should incorporate a one-way air system to prevent contaminated air entering the face mask during connection or disconnection. The air supply should be treated to ensure a temperature and level of humidity that are comfortable for the operator. The air source could be a high pressure fan or an air compressor. If an air compressor is used, it should be of the oil-free type or have suitable oil removal filters fitted;
- a self-contained breathing apparatus (SCBA) or powered air purifying respirator (PAPR) that is securely attached to the operator's belt and connects to the operator's face mask. This system draws air from the room in which the operator is working and the air supply is delivered to the face mask by means of a battery-driven fan. The AR provides superior protection to the PAPR apparatus;
- for zones with lower contamination levels, a half-mask high efficiency particulate air filter (HEPA) cartridge respirator or N95-type paper filter mask may be acceptable.

6.3 The selection of the respirator type is based on the relationship between the accepted OEL and the respirator-certified protection factor (PF).

6.4 The air supplies should be filtered through a final filter, which should be a HEPA filter rated as an H13 filter according to EN 1822 (European Norm). The supply of breathing air into the face mask and/or protective suit should result in the interior of the mask and suit being at a positive pressure relative to the facility environment.

6.5 Central breathing air supply systems should have a 100% back-up system in the event of the main system failing. This could be in the form of a gas bottle system with at least 5 minutes supply. Changeover from the normal supply to the back-up supply should be automatic. The system should have a monitoring system and send alarm signals to a permanently manned location in the following situations:

- failure of main air supply;
- temperature out of specification (OOS);
- humidity OOS;
- carbon dioxide (CO₂) OOS;
- carbon monoxide (CO) OOS; and
- sulfur dioxide (SO₂) OOS.

6.6 Breathing air should be filtered by means of pre-filters, coalescing filters and final filters to have the minimum air quality specifications of ISO 8573-1 3-9-1 and EN 12021:1999.

6.7 Where air is delivered through a central system the piping should not cause any contamination to be liberated into the air stream. Stainless steel piping is preferred. The final filters should be as close as possible to the operator connection points. The operator hose connection to the air supply should be a dedicated connection specific to the breathing air system (to avoid inadvertent connection to a different gas system).

7. Environmental protection

7.1 Due to the hazardous nature of the products being handled in the facility, neither the product nor its residues should be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.

7.2 The external atmosphere and the public in the vicinity of the facility should be protected from possible harm from hazardous substances.

7.3 If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.

7.4 Exhaust air filtration to ensure environmental protection is discussed in section 11.

8. Facility layout

8.1 The premises should be designed and constructed to prevent the ingress or egress of contaminants. In drawing up the facility design, attention should be paid to the level of containment provided by the equipment.

8.2 The link between the interior and exterior of the premises should be through airlocks (PAL and/or MAL), changing rooms, pass boxes, pass-through hatches, decontamination devices, etc. These entry and exit doors for materials and personnel should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.

8.3 The changing rooms should have an arrangement with a step-over-bench. The facilities on the exit side should incorporate showers for the operators.

8.4 The premises should be laid out and designed so as to facilitate the required pressure cascades and containment.

8.5 The premises (and equipment) should be appropriately designed and installed to facilitate cleaning and decontamination.

8.6 The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) to ensure that the designation and conditions of use of all the rooms are correctly shown.

8.7 The flow of people and products should be clearly marked on the layouts and plans.

8.8 The activities carried out in the vicinity of the site should be indicated.

8.9 Plans should describe the ventilation systems, indicating inlets and outlets, in relation to other facility air inlet and outlet points.

8.10 The facility should be a well-sealed structure with no air leakage through ceilings, cracks or service areas.

8.11 Areas of the facility where exposed product presents a risk should be maintained at a negative air pressure relative to the environment.

9. **Air-handling systems**

9.1 The HVAC system should be appropriately designed, installed and maintained to ensure protection of product, personnel and the environment.

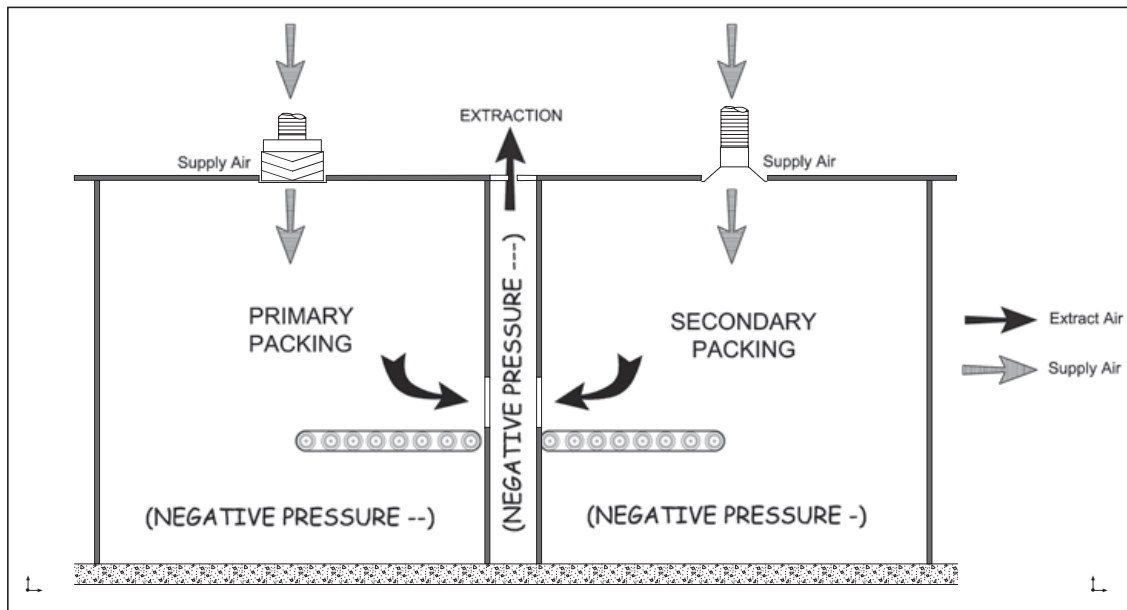
9.2 The principles of airflow direction, air filtration standards, temperature, humidity and related parameters should comply with the minimum requirements as set out in Annex 2 of the fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2006 (2).

9.3 Facilities and premises dealing with hazardous substances should have the following basic air-handling characteristics:

- There should be no direct venting of air to the outside.
- Air-conditioning or ventilation should result in a negative pressure relative to the outside. Air pressure differentials should be such that there is no uncontrolled flow of air between the work area and the external environment.
- Appropriate air pressure alarm systems should be provided to warn of any pressure cascade reversal or loss of design pressure status. The appropriate design, alert and action limits should be in place. System redundancies should be in place to respond appropriately to pressure cascade failure.
- The starting and stopping of the supply and exhaust air fan should be synchronized such that the premises remain at a negative pressure during start-up and shut-down.
- The air pressure cascade within the facility, although negative relative to the environment, should comply with normal pharmaceutical pressure cascade requirements with regards to product protection, dust containment and personnel protection.
- Visual indication of the status of room pressures should be provided in each room.
- Air should be exhausted to the outside through HEPA filters and not be recirculated except to the same area, and provided that a further HEPA filtration stage is applied to the return air. Where HEPA filters are

Figure 1

Typical airflow pattern for contaminant



mentioned in these guidelines, this refers to HEPA filters with a minimum rating of H13 according to EN 1822.

- Where possible, single-pass air-handling systems with no recirculation should be provided.
- Exhaust air or return air should be filtered through a safe-change or bag-in-bag-out filter housing. The filter housing should contain pre-filters and HEPA filters, both of which should be removable with the safe bagging system.
- Changing rooms should be supplied with air filtered to the same standard as that for the work area they serve.
- Airlocks, pass-through hatches, etc., should have supply and extract air to provide the necessary air pressure cascade and containment. The final, or containment perimeter, airlock or pass-through hatch bordering on an external or non-GMP area should be at a positive pressure relative to the environment, to prevent the ingress of contaminants to the facility.
- If the facility provides insufficient containment, and operators' garments are contaminated with dust, the operators leaving the containment area should pass through a decontamination system, e.g. air showers or a mist shower system, to assist with removing or controlling dust particles on their garments. Operators should follow this route before de-gowning to use the ablutions or canteen facilities. All garments leaving the facility for laundering should be safely bagged. Appropriate means for protecting laundry staff and prevention of contamination of other garments from non-hazardous facilities should be in place.

9.4 If required, appropriate measures should be taken to prevent airflow from the primary packing area (through the conveyor “mouse hole”) to the secondary packing area.

Note: This could be overcome by having a pass-through chamber over the “mouse hole”, which is maintained at a negative pressure to both primary and secondary packing. This typical arrangement is illustrated in Figure 1. This principle can be applied to other situations where containment from two sides is required.

9.5 Where possible, HEPA filters in the supply air system should be terminally mounted to provide protection against back-flow cross-contamination in the event of a failure in the supply airflow.

9.6 In some cases consideration can be given to the use of biosafety cabinets, isolation systems or glove boxes as a means for containment and operator protection.

9.7 There should be a system description including schematic drawings detailing the filters and their specifications, the number of air changes per hour, pressure gradients, clean room classes and related specifications. These should be available for inspection.

9.8 There should be an indication of pressure gradients that are monitored by means of digital or analogue pressure indicators.

9.9 Consideration should be given to providing an emergency power supply, e.g. diesel generators, to ensure that safe operation of the premises and systems can be maintained at all times.

10. **Air-handling units**

10.1 The air-handling units (AHUs) supplying air to the facility should conform to AHU requirements as detailed in *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials (1)* and *Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms (2)* and the filtration should be consistent with the zone concepts and product protection required.

10.2 The decision to use return air or recirculated air should be made on the basis of a risk assessment.

10.3 Where a full fresh-air or single-pass system is used, an energy recovery wheel could be considered. In such cases, there should not be any potential for air leakage between the supply air and exhaust air as it passes through the wheel. The relative pressures between supply and exhaust air systems should be such that the exhaust-air system operates at a lower

pressure than the supply system. (Alternatives to the energy recovery wheel, such as crossover plate heat exchangers, heat pipes and water coil heat exchangers, may be used.)

10.4 Risk management principles should be applied to address the potential of cross-contamination where energy wheels are used.

10.5 If return air is to be recirculated it should pass through a safe change filtration system before being introduced back into the supply AHU. The return air fan could form part of the AHU; however, the safe change filter should be a dedicated unit. With this arrangement the return air passes through two sets of HEPA filters in series, i.e. the return air filters in the safe change housing and the supply air HEPA filters. The supply air HEPA filters could either be located in the AHU or terminally located at the supply diffusers, depending on the clean room classification of the facility.

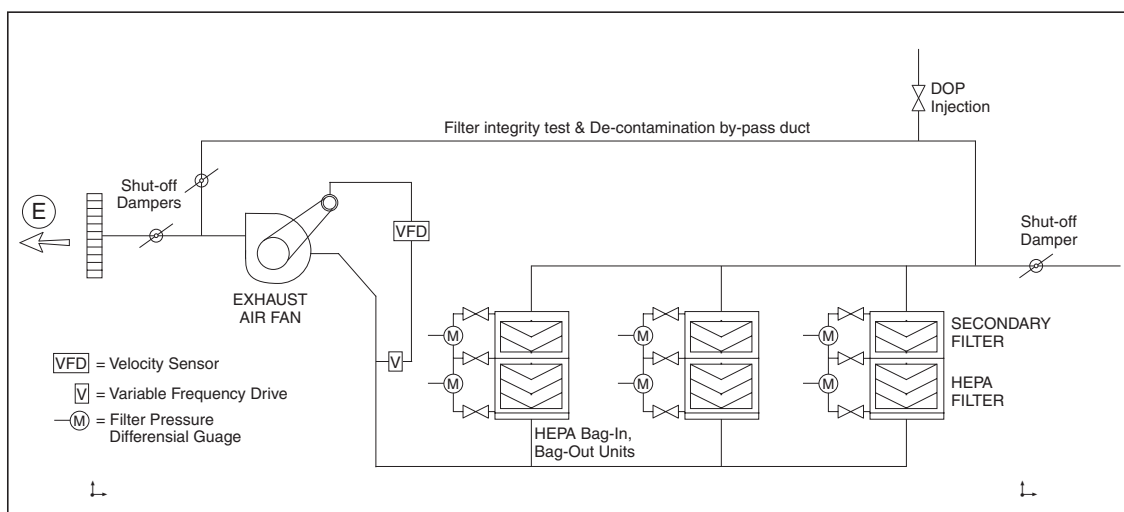
10.6 The starting and stopping of the supply and exhaust air fans, and associated system ventilation fans, should be synchronized such that the premises retain their design pressure and flow relationships during start-up and shut-down. Processing should stop when the fans are not running. This fan interlock sequence should also apply if any fan should fail, to ensure that there is no airflow reversal in the system.

11. Safe change filter housings

11.1 Safe change or bag-in-bag-out filter housings should be suitably designed to provide operator protection and to prevent dust from the filters entering the atmosphere when filters are changed.

Figure 2

Safe change filter bypass arrangement



11.2 The final filters on the safe change unit should be HEPA filters with at least an H13 classification according to EN 1822 filter standards. For dusty return, air pre-filtration may also be required to prolong the life of the HEPA filters. The pre-filtration filters should also be removable through the bag-in-bag-out method.

11.3 For exhaust systems where the discharge contaminant is considered particularly hazardous, two banks of HEPA filters in series should be considered to provide additional protection should the first filter fail.

11.4 All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading and remaining lifespan of the filters. Connection to these gauges should be copper or stainless steel and not plastic tubing, which could perish causing a contamination hazard. The tube connections on the filter casing should be provided with stopcocks, for safe removal or calibration of gauges.

11.5 Monitoring of filters should be done at regular intervals to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination.

11.6 Computer-based data monitoring systems may be installed to monitor filter condition.

11.7 Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.

11.8 Installed filter leakage tests should be performed in accordance with ISO 14644-3. Injection ports (upstream) and access ports (downstream) should, therefore, be provided for this purpose.

11.9 The exhaust air fan on a safe change filter system should be located after the filters so that the filter housing is maintained at a negative pressure. This poses a difficulty when carrying out filter integrity tests, and for this reason a bypass damper system should be provided, as illustrated in Figure 2, so that air can be circulated through the HEPA filters, while the scanning ports are open. Alternatively an independent booster fan system can be used, with appropriate shut-off dampers.

11.10 The bypass arrangement as shown in Figure 2 also permits decontamination of the filters by means of circulation of a sanitizing agent.

11.11 All exhaust systems from the facility, including dust extraction systems, vacuum system exhaust, fluid bed drier exhaust and coating pan exhaust, should be passed through safe change filter housings before being exhausted to the atmosphere.

11.12 All exhaust points outside the building should be located as far as possible from air entry points, and exit points should be at a high level to minimize the possibility of re-entrainment of exhaust air. Dominant and seasonal wind directions should be taken into account when positioning exhaust and supply points.

11.13 Where excessively dust-laden air is handled, a dust collector or bag house should be considered, with the dust collector being located in an enclosed room maintained at a negative pressure. Access control, maintenance staff, personal protection equipment (PPE) and breathing air systems should then be provided to protect the operators during removal of dust from the collector bins.

11.14 Portable vacuum cleaners and portable dust collectors should be fitted with H13 HEPA filters. These types of units should be emptied and cleaned in a room which is under negative pressure relative to the environment. Personnel should be provided with suitable PPE.

11.15 Records of the safe disposal of all contaminated filters and dust should be kept.

12. **Personnel decontamination systems**

12.1 If required, a means of preventing contaminants from leaving the facility on the garments of personnel should be provided. This could be in the form of an air shower; mist shower, water shower or appropriate device.

12.2 An air shower comprises an airlock where high velocity air is supplied through air nozzles (e.g. from the sides of the airlock) in order to dislodge dust particles. Air extraction grilles (e.g. at low level) should draw the air away and return it to the filtration system. Some air showers may also incorporate a vertical unidirectional airflow section at the exit end, to flush contaminants away.

Note: When air showers are used these should be correctly designed to effectively extract dust.

Air filtration of the supply air and return or exhaust air should comply with the same filtration standards as used in the manufacturing facility. Normally the fan should be activated by opening the door as the operator enters the shower, with a timing device on the exit door interlock to allow sufficient time for the decontamination process to be effective.

12.3 Flushing devices similar to air or mist showers for personnel could be used at material exits to assist with removing contaminants.

12.4 Wet mist or fog decontamination systems for operators can be employed for deactivating contaminants on the operator's garments, or

causing contaminants to adhere to the garments so that they are not easily liberated.

12.5 Personnel should change into clean garments after having taken a shower.

13. **Effluent treatment**

13.1 Liquid and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.

13.2 All effluent should be disposed of in a safe manner, and the means of disposal should be documented. Where external contractors are used for effluent disposal they should have certification authorizing them to handle and treat hazardous products.

14. **Maintenance**

14.1 The efficient and safe operation of a facility handling hazardous materials is reliant on regular maintenance being carried out, to ensure that all parameters remain within specified tolerances. See *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials (1)* or WHO Technical Report Series, No. 937, Annex 2, section 8.3 (2) for further details on maintenance.

15. **Qualification and validation**

15.1 System qualification and validation should be carried out as described in other WHO guidelines.

References

1. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2, 2nd updated ed. Good manufacturing practices and inspection.* Geneva, World Health Organization, 2007.
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4. WHO good manufacturing practices for sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report.* Geneva, World Health Organization, 2010, Annex 4 (WHO Technical Report Series, No. 957).
5. ISO: International Standard. *Clean rooms and associated controlled environments. ISO 14644.* Geneva, International Organization for Standardization.

Annex 4

WHO good manufacturing practices for sterile pharmaceutical products

Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations in its thirty-sixth report in 1999 adopted *WHO good manufacturing practices for sterile pharmaceutical products* (WHO Technical Report Series, No. 902, 2002, Annex 6) (http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf); and published in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2. 2nd updated ed. Good manufacturing practices and inspection* (2007) (1).

Following implementation of these WHO good manufacturing practices (GMP) within the context of the WHO Prequalification Programme, a proposal for revision is being submitted to take into consideration new developments. The proposal for revision of the above-mentioned guidance is being made to bring the WHO GMP into line with International Standardization Organization standard ISO 14644-1 (2) and recent practices of the United States (3), Japan (4), the European Union (5) and the Pharmaceutical Inspection Co-operation Scheme.

- New chapters on Isolator technology and Blow/fill/seal technology have been added to the document.
- The chapter on Finishing of sterile products has been amended and provisions have been given for capping of vials.
- The chapter entitled Manufacture of sterile preparations has been amended and provisions have been given for clean room and clean-air device monitoring.

Implementation of these new practices may need to be undertaken for certain parts using a step-wise approach, especially the part relating to the provision for capping in a clean or sterile environment, as this is currently not implemented in most industries.

On the basis of the above, the following text is proposed to replace the previously published guidance.

WHO good manufacturing practices for sterile pharmaceutical products

1. General considerations
2. Quality control
3. Sanitation
4. Manufacture of sterile preparations
5. Sterilization
6. Terminal sterilization
7. Aseptic processing and sterilization by filtration
8. Isolator technology
9. Blow/fill/seal technology
10. Personnel
11. Premises
12. Equipment
13. Finishing of sterile products

References

1. **General considerations**

1.1 The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.

1.2 The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within the clean area. These areas are classified into four grades (see section 4).

Manufacturing operations are divided here into two categories:

- first, those where the product is terminally sterilized; and
- second, those which are conducted aseptically at some or all stages.

2. **Quality control**

2.1 The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.

2.2 Samples taken for sterility testing should be representative of the whole of the batch but should, in particular, include samples taken from parts of the batch considered to be most at risk of contamination, for example:

- for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;
- for products that have been heat sterilized in their final containers, consideration should be given to taking samples from that part of the load that is potentially the coolest.

2.3 The sterility of the finished product is assured by validation of the sterilization cycle in the case of terminally sterilized products, and by “media simulation” or “media fill” runs for aseptically processed products. Batch-processing records and, in the case of aseptic processing, environmental quality records, should be examined in conjunction with the results of the sterility tests. The sterility test procedure should be validated for a given product. Pharmacopoeial methods should be used for the validation and performance of the sterility test. In those cases where parametric release has been authorized in place of sterility testing special attention should be paid to the validation and the monitoring of the entire manufacturing process.

2.4 For injectable products the water for injection and the intermediate, if appropriate, and finished products should be monitored for endotoxins,

using an established pharmacopoeial method that has been validated for each type of product. For large-volume infusion solutions, such monitoring of water or intermediates should always be done, in addition to any tests required by an approved monograph for the finished product. When a sample fails a test, the cause of the failure should be investigated and necessary action should be taken. Alternative methods to those in the pharmacopoeias may be used if they are validated, justified and authorized.

2.5 The use of rapid microbiological methods to replace the traditional microbiological methods, and to obtain earlier results on the microbiological quality of, for example, water, the environment or bioburden, could be considered if appropriately validated and if a comparative assessment of the proposed rapid method is performed against the pharmacopoeial method.

3. **Sanitation**

3.1 The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with an approved written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be regularly undertaken to detect contamination or the presence of an organism against which the cleaning procedure is ineffective. Interactions between different cleaning materials should be validated. Appropriate cleaning validation should be carried out to ensure disinfectant residuals can be detected and are removed by the cleaning process.

3.2 Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilized. Disinfectants and detergents used in grade A and B areas should be sterile before use.

3.3 A disinfectant programme should also include a sporicidal agent since many common disinfectants are ineffective against spores. The effectiveness of cleaning and disinfectant procedures should be demonstrated.

3.4. Fumigation of clean areas may be useful for reducing microbial contamination in inaccessible places.

4. **Manufacture of sterile preparations**

4.1 Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate level of environmental cleanliness in the operational state to minimize the risks of particulate or microbial contamination of the product or materials being handled.

4.2 Detailed information on methods for determining the microbiological and particulate cleanliness of air, surfaces, etc., is not given in these guidelines.

ISO 14644-1 (2) should be used for classification of cleanliness according to concentration of airborne particles (determination of number of sample locations, calculation of sample size and evaluation of classification from the data obtained). Table 1 should also be used to define the levels to be used as the basis for monitoring clean areas for airborne particles.

4.3 For the manufacture of sterile pharmaceutical preparations, four grades of clean areas are distinguished as follows:

- *grade A*: The local zone for high-risk operations, e.g. filling and making aseptic connections. Normally such conditions are achieved by using a unidirectional airflow workstation. Unidirectional airflow systems should provide a homogeneous air speed of 0.36–0.54 m/s (guidance value) at a defined test position 15–30 cm below the terminal filter or air distributor system. The velocity at working level should not be less than 0.36 m/s. The uniformity and effectiveness of the unidirectional airflow should be demonstrated by undertaking airflow visualization tests;
- *grade B*: In aseptic preparation and filling, this is the background environment for the grade A zone;
- *grades C and D*: Clean areas for carrying out less critical stages in the manufacture of sterile products or carrying out activities during which the product is not directly exposed (i.e. aseptic connection with aseptic connectors and operations in a closed system).

A unidirectional airflow and lower velocities may be used in closed isolators and glove boxes.

4.4 In order to reach the B, C and D air grades the number of air changes should be appropriate for the size of the room and the equipment and personnel present in it.

4.5 High-efficiency particulate air (HEPA) filters should be subjected to an installed filter leakage test in accordance with ISO 14644-3 (6) at a recommended interval of every 6 months, but not exceeding 12 months. The purpose of performing regular leak tests is to ensure the filter media, filter frame and filter seal are free from leaks. The aerosol selected for HEPA leak testing should not support microbial growth and should be composed of a sufficient number or mass of particles. HEPA filter patching is allowed at the filter manufacturer and in situ operation provided that the patch sizes and procedures follow the recommendations of ISO 1822-4 (7).

4.6 Clean room and clean-air device classification

4.6.1 Clean rooms and clean-air devices should be classified in accordance with ISO 14644 (2, 6–9).

4.6.1.1 Classification should be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each grade is given in Table 1.

Table 1

Maximum permitted airborne particle concentration

	Maximum permitted number of particles per m³ greater than or equal to the tabulated size			
	At rest^a		In operation^b	
Grade	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

^a The “at rest” state is the condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

^b The “in operation” state is the condition where the installation is functioning in the defined operating mode and the specified number of personnel is present. The areas and their associated environmental control systems should be designed to achieve both the “at rest” and “in operation” states.

4.6.2 For classification purposes, ISO 14644-1 (2) methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method for evaluation of the data collected. For classification of grade A zones (at rest and operational) and grade B zones (at rest), the minimum sample volume is based on the ISO 5 limit for the number of particles $\geq 0.5 \mu\text{m}$ (3520). Similarly, for classification of grade B (operational), grade C (at rest and operational), and grade D (at rest), the minimum sample volume is based on the class limits for particles $\geq 0.5 \mu\text{m}$ shown in Table 1.

For classification purposes in grade A zones, a minimum sample volume of 1 m³ should be taken per sample location. Referring to Table 1, for grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles $\geq 5.0 \mu\text{m}$. For grade B (at rest) the airborne particle classification is ISO 5 for both particle sizes considered. For grade C (at rest and in operation) the airborne particle classification is ISO 7 and ISO 8, respectively. For grade D (at rest) the airborne particle classification is ISO 8. For classification purposes ISO 14644-1 (2) methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest particle size considered and the method of evaluation of the data collected. The sample volume should be determined according to ISO 14644-1 (2) clause B.4.2. However, for lower grades

(grade C in operation and grade D at rest) the sample volume per location should be at least 2 litres and the sample time per location should be not less than 1 minute. There should not be less than 3 sample locations per room.

4.6.3 Portable particle counters with a short length of sample tubing should be used for classification purposes to avoid the loss of particles $\geq 5.0 \mu\text{m}$. Isokinetic sample heads should be used in unidirectional airflow systems.

4.6.4 “In operation” classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. ISO 14644-2 (8) provides information on testing to demonstrate continued compliance with the assigned cleanliness classification.

4.7 Clean room and clean-air device monitoring

4.7.1 Clean rooms and clean-air devices should be routinely monitored while in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean-air devices.

4.7.2 For grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, for example, live organisms and radiological hazards. In such cases monitoring during routine equipment set-up operations should be undertaken before exposure to the risk. Monitoring during simulated operations should also be performed. The grade A zone should be monitored at a frequency and sample size such that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of $\geq 5.0 \mu\text{m}$ particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

4.7.3 It is recommended that a similar system be used for grade B zones, although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent grade A and B zones. The grade B zone should be monitored at a frequency and with a sample size such that changes in levels of contamination and any deterioration of the system would be captured and alarms triggered if alert limits are exceeded.

4.7.4 Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points

connected by manifold to a single particle counter; or multiple small particle counters located near monitoring points and networked to a data acquisition system. Combinations of systems can also be used. The system selected should be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing should be considered in the context of particle losses in the tubing. The selection of the monitoring system should take account of any risk presented by the materials used in the manufacturing operation, for example, those involving live organisms or radiopharmaceuticals.

4.7.5 The sizes of samples taken for monitoring purposes using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean-air devices.

4.7.6 The airborne particle conditions given in Table 1 for the “at rest” state should be achieved in the absence of the operating personnel after a short “clean-up” or “recovery” period of about 15–20 minutes (guidance value), after completion of the operations. The particulate conditions given in Table 1 for grade A “in operation” should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. The “clean-up” or “recovery” test should demonstrate a change in particle concentration by a factor of 100 within the prescribed time (ISO 14644-3 clause B.12) (6).

4.7.7 In order to demonstrate control of the cleanliness of the various clean areas during operation, they should be monitored for airborne particles and microbial contamination. In addition to “at rest” and “in operation” classification, airborne particles should be monitored periodically “in operation” at critical locations. The sampling plan need not be the same as that used for classification. Locations and sample sizes should be determined based on an assessment of the process and contamination risk.

4.7.8 The monitoring of grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended “clean-up period” should be attained.

4.7.9 Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.

4.7.10 Examples of operations to be carried out in the various grades are given in Table 2 (see also sections 4.14–4.22).

Table 2

Examples of operations to be carried out in the various grades

Grade	Examples of operations for terminally sterilized products (see sections 4.14–4.17)
A	Filling of products when unusually at risk
C	Preparation of solutions when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for aseptic preparations (see sections 4.18–4.22)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

4.8 To control the microbiological cleanliness of the cleanliness grades A–D in operation the clean areas should be monitored. Where aseptic operations are performed, monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitization.

4.9 Levels of detection of microbial contamination should be established for the purpose of setting alert and action levels and for monitoring the trends in environmental cleanliness in the facility. Limits expressed in colony-forming units (CFU) for the microbiological monitoring of clean areas in operation are given in Table 3. The sampling methods and numerical values included in the table are not intended to represent specifications, but are for information only.

Table 3

Recommended limits for microbial contamination^a

Grade	Air sample (CFU/m³)	Settle plates (diameter 90 mm) (CFU/4 hours)^b	Contact plates (diameter 55 mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

CFU, colony-forming units.

^a These are average values.

^b Individual settle plates may be exposed for less than 4 hours.

4.10 Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If the action limits are exceeded or a trend is identified in the alert levels, investigation should be initiated and the appropriate corrective actions should be taken, as prescribed in the operating procedures.

4.11 The area grades as specified in sections 4.12 to 4.20 should be selected by the manufacturer on the basis of the nature of the process operations being performed and validation runs (e.g. aseptic media fills or others types of process simulations) are used to establish processing hold times and a maximum fill duration. The determination of an appropriate process area environment and a time limit should be based on the microbial contamination (bioburden) found.

terminally sterilized products

4.12 Components and most products should be prepared in at least a grade D environment to ensure low microbial bioburden and particulate counts prior to filtration and sterilization. Where the product is at unusual risk of microbial contamination (e.g. because it actively supports microbial growth, must be held for a long period before sterilization, or is necessarily processed mainly in open vessels), the preparation should generally be done in a grade C environment.

4.13 The filling of products for terminal sterilization should generally be done in at least a grade C environment.

4.14 Where the product is at unusual risk of contamination from the environment (e.g. because the filling operation is slow, the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing), the filling should be done in a grade A zone with at least a grade C background.

4.15 The preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilization.

Aseptic preparation

4.16 Components after washing should be handled in at least a grade D environment. The handling of sterile starting materials and components, unless subjected to sterilization or filtration through a microorganism-retaining filter later in the process, should be undertaken in a grade A environment with a grade B background.

4.17 The preparation of solutions which are to be sterile-filtered during the process should be undertaken in a grade C environment (unless a closed system is used, in which case a Class D environment may be justifiable).

If not sterile-filtered (therefore an aseptic manipulation) the preparation of materials and products should be undertaken in a grade A environment with a grade B background.

4.18 The handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, should be undertaken in a grade A environment with a grade B background.

4.19 The transfer of partially closed containers, as used in freeze-drying, before stoppering is completed, should be undertaken either in a grade A environment with a grade B background or in sealed transfer trays in a grade B environment.

4.20 The preparation and filling of sterile ointments, creams, suspensions and emulsions should be undertaken in a grade A environment with a grade B background when the product is exposed and is not subsequently filtered.

Processing

4.21 Precautions to minimize contamination should be taken during all processing stages, including the stages before sterilization.

4.22 In general, preparations containing live microorganisms should not be made, nor should containers be filled in areas used for the processing of other pharmaceutical products. However, if the manufacturer can demonstrate and validate effective containment and decontamination of the live microorganisms, the use of multiproduct facilities may be justifiable. Vaccines consisting of dead organisms or of bacterial extracts may be dispensed into containers in the same premises as other sterile pharmaceutical products, provided that the inactivation procedure has been properly validated.

When multiproduct facilities are used to manufacture sterile preparations containing live microorganisms and other sterile pharmaceutical products, the manufacturer should demonstrate and validate the effective decontamination of the live microorganisms, in addition to precautions taken to minimize contamination.

4.23 Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium.

4.24 The process simulation test should imitate as closely as possible the routine aseptic manufacturing steps except where the activity may lead to any potential microbial contamination.

4.25 Process simulation tests should be performed as part of validation by running three consecutive satisfactory simulation tests. These tests should be repeated at defined intervals and after any significant modification to

the heating, ventilation and air-conditioning (HVAC)-system, equipment or process. Process simulation tests should incorporate activities and interventions known to occur during normal production as well as the worst-case situation. The process simulation tests should be representative of each shift and shift changeover to address any time-related and operational features.

4.26 The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following should apply:

- when filling fewer than 5000 units, no contaminated units should be detected;
- when filling 5000–10 000 units:
 - one contaminated unit should result in an investigation, including — consideration of a repeat media fill,
 - two contaminated units are considered cause for revalidation following investigation;
- when filling more than 10 000 units:
 - one contaminated unit should result in an investigation,
 - two contaminated units are considered cause for revalidation following investigation.

4.27 For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated. Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

4.28 Care should be taken to ensure that any validation does not compromise the processes.

4.29 Water sources, water-treatment equipment and treated water should be monitored regularly for chemicals, biological contamination and contamination with endotoxins to ensure that the water complies with the specifications appropriate to its use. Records should be maintained of the results of the monitoring and of any action taken (10).

4.30 Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum and the movement of personnel should be controlled and methodical, so as to avoid excessive shedding of particles and organisms due to over-vigorous activity. As far as possible, personnel should be excluded from grade A zones. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn and to reduce the risk of contamination liberated from the personnel.

4.31 The presence of containers and materials liable to generate fibres should be minimized in clean areas and avoided completely when aseptic work is in progress.

4.32 Components, bulk-product containers and equipment should be handled after the final cleaning process in such a way as to ensure that they are not recontaminated. The stage of processing of components as well as the bulk-product containers and equipment should be properly identified.

4.33 The interval between the washing and drying and the sterilization of components, bulk-product containers and equipment, as well as between sterilization and use, should be as short as possible and subject to a time-limit appropriate to the validated storage conditions.

4.34 The time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retaining filter should be as short as possible. A maximum permissible time should be set for each product that takes into account its composition and the prescribed method of storage.

4.35 Any gas that is used to purge a solution or blanket a product should be passed through a sterilizing filter.

4.36 The bioburden should be monitored before sterilization. There should be working limits on contamination immediately before sterilization, which are related to the efficiency of the method to be used. Bioburden assay should be performed on each batch for both aseptically filled products and terminally sterilized products. Where overkill sterilization parameters are set for terminally sterilized products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assay should be performed on each batch and considered as an in-process test. Where appropriate, the level of endotoxins should be monitored. All solutions, in particular large-volume infusion fluids, should be passed through a microorganism-retaining filter, if possible sited immediately before filling.

4.37 Components, bulk-product containers, equipment, and any other articles required in a clean area where aseptic work is in progress, should be sterilized and wherever possible passed into the area through double-ended sterilizers sealed into the wall. Other procedures that prevent the introduction of contamination may be acceptable in some circumstances.

4.38 The efficacy of any new processing procedure should be validated and the validation should be repeated at regular intervals thereafter or when any significant change is made in the process or equipment.

5. Sterilization

5.1 Whenever possible products intended to be sterile should be terminally sterilized by heat in their final container. Where it is not possible to carry out terminal sterilization by heating due to the instability of a formulation or incompatibility of a pack type (necessary to the administration of the product, e.g. plastic eye-dropper bottles), a decision should be taken to use an alternative method of terminal sterilization following filtration and/or aseptic processing.

5.2 Sterilization can be achieved by the use of moist or dry heat, by irradiation with ionizing radiation (noting that ultraviolet irradiation is not normally an acceptable method of sterilization), by ethylene oxide (or other suitable gaseous sterilizing agents), or by filtration with subsequent aseptic filling of sterile final containers. Each method has its advantages and disadvantages. Where possible and practicable, heat sterilization is the method of choice. In any case the sterilization process must be in accordance with the marketing and manufacturing authorizations.

5.3 The microbial contamination of starting materials should be minimal and their bioburden should be monitored before sterilization. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.

5.4 All sterilization processes should be validated. Particular attention should be paid when the adopted sterilization method is not in accordance with pharmacopoeial standards or other national standards, or when it is used for a preparation that is not a simple aqueous or oily solution, for example, colloidal suspensions.

5.5 Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators, where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

5.6 For effective sterilization the whole of the material should be subjected to the required treatment and the process should be designed to ensure that this is achieved.

5.7 Biological indicators should be considered only as an additional method of monitoring the sterilization process. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If they are used, strict precautions should be taken to avoid any transfer of microbial contamination from them.

5.8 There should be a clear means of differentiating products that have not been sterilized from those which have. Each basket, tray, or other carrier of products or components should be clearly labelled with the name of the material, its batch number and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used where appropriate to indicate whether or not a batch (or sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the batch is in fact sterile.

5.9 Validated loading patterns should be established for all sterilization processes.

5.10 Sterilization records should be available for each sterilization run. They should be approved as part of the batch-release procedure.

6. Terminal sterilization

Sterilization by heat

6.1 Each heat-sterilization cycle should be recorded by means of appropriate equipment of suitable accuracy and precision, e.g. on a time/temperature chart with a suitably large scale. The temperature should be recorded by a probe situated at the coolest part of the load or loaded chamber, this point having been determined during the validation; the temperature should preferably be checked against a second independent temperature probe located at the same position. Sterilization records should be available for each sterilization run and should be approved as part of the batch release procedure. Chemical or biological indicators may also be used but should not take the place of physical controls.

6.2 Sufficient time should be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time is started. This time should be determined for each type of load to be processed.

6.3 After the high-temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized.

Sterilization by moist heat

6.4 Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator.

The reading of the independent temperature indicator should be routinely checked against the reading on the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilization period. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.

6.5 The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows the removal of air and the penetration of steam but prevents recontamination after sterilization. Specially designed autoclavable stainless steel containers, that allow steam to enter and air to leave, can also be used. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.

6.6 Care should be taken to ensure that the steam used for sterilization is of suitable quality (chemical, microbiological and endotoxin analysis of condensate and physical examination of steam (such as dryness, superheat, and non-condensable gases)) and does not contain additives at a level that could cause contamination of the product or equipment. Steam used for sterilization should be tested regularly.

Sterilization by dry heat

6.7 Sterilization by dry heat may be suitable for non-aqueous liquids or dry-powder products.

The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. If air is supplied it should be passed through a microorganism-retaining filter (e.g. a HEPA filter). Where sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins are required as part of the validation.

Sterilization by radiation

6.8 Sterilization by radiation is used mainly for heat-sensitive materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilization.

6.9 If sterilization by radiation is done by an outside contractor, the manufacturer is responsible for ensuring that the requirements of section 6.8 are met and that the sterilization process is validated.

6.10 During the sterilization procedure the radiation dose should be measured. The dosimeters used for this purpose should be independent of

the dose rate and should provide a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbance should be read shortly after exposure to radiation. Radiation-sensitive colour discs may be used to differentiate between packages that have been subjected to irradiation and those that have not; they are not indicators of successful sterilization. The information obtained should constitute part of the batch record.

6.11 Validation procedures should ensure that consideration is given to the effects of variations in the density of the packages.

6.12 Material-handling procedures should prevent any mix-up of irradiated and non-irradiated materials. Each package should carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment.

6.13 The total radiation dose should be administered within a predetermined period.

Sterilization by gases and fumigants

6.14 Sterilization by gases and fumigants should only be used for finished products where there is no suitable alternative.

6.15 Various gases and fumigants may be used for sterilization (e.g. ethylene oxide and hydrogen peroxide vapour). Ethylene oxide should be used only when no other method is practicable. During process validation it should be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material concerned. These limits should be incorporated in the specifications.

6.16 Direct contact between gas and microorganisms is essential; precautions should therefore be taken to avoid the presence of organisms likely to be enclosed in materials such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

6.17 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. This requirement should be balanced against the need to minimize the waiting time before sterilization.

6.18 Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed

throughout the load. The information thus obtained should form part of the batch record.

6.19 Biological indicators should be stored and used according to the manufacturer's instructions and their performance checked by positive controls.

6.20 For each sterilization cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration. The pressure and temperature should be recorded on a chart throughout the cycle. The records should form part of the batch record.

6.21 After sterilization, the load should be stored in a controlled manner in ventilated conditions to allow concentrations of residual gas and reaction products to fall to their prescribed levels. This process should be validated.

7. Aseptic processing and sterilization by filtration

7.1 The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which has been sterilized by one of the above methods (see sections 5 and 6).

7.2 The operating conditions should be such as to prevent microbial contamination.

7.3 In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to:

- the environment;
- personnel;
- critical surfaces;
- container/closure sterilization and transfer procedures;
- the maximum holding period of the product before filling into the final container; and
- the sterilizing filter.

7.4 Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22 micron (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment. Filtration alone is not considered sufficient when sterilization in the final container is possible. Of the methods currently available, steam sterilization is to be preferred.

7.5 Owing to the potential additional risks of the filtration method as compared with other sterilization processes, a double-filter layer or second filtration through a further sterilized microorganism-retaining filter immediately prior to filling may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

7.6 The fibre-shedding characteristics of filters should be minimal (virtually zero). Asbestos-containing filters should not be used under any circumstances.

7.7 The integrity of the sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from these during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals. Consideration should be given to increased monitoring of filter integrity in processes that involve harsh conditions, e.g. the circulation of high-temperature air.

7.8 The same filter should not be used for more than one working day unless such use has been validated.

7.9 The filter should not affect the product either by removing ingredients from it or by releasing substances into it.

8. Isolator technology

8.1 The use of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbial contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for each zone can be realized. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from single-door to double-door designs to fully-sealed systems incorporating sterilization mechanisms.

8.2 The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high-risk manipulations, although it is recognized that unidirectional airflow may not exist in the working zone of all isolators and transfer devices.

8.3 The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled, and for aseptic processing it should be at least grade D.

8.4 Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example, the quality of the air inside and outside (background) the isolator, sanitization of the isolator, the transfer process and isolator integrity.

8.5 Monitoring should be done routinely and should include frequent leak testing of the isolator and the glove/sleeve system.

9. **Blow/fill/seal technology**

9.1 Blow/fill/seal units are purpose-built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A or B clothing is used. The environment should comply with the viable and non-viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products which are terminally sterilized should be installed in at least a grade D environment.

9.2 Because of this special technology, particular attention should be paid to at least the following:

- equipment design and qualification;
- validation and reproducibility of cleaning-in-place and sterilization-in-place;
- background clean room environment in which the equipment is located;
- operator training and clothing; and
- interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

10. **Personnel**

10.1 Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. As far as possible, inspections and controls should be conducted from outside such areas.

10.2 All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive initial and regular training in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology. When outside

staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.

10.3 Staff who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.

10.4 High standards of personal hygiene and cleanliness are essential and personnel involved in the manufacture of sterile preparations should be instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. The action to be taken in respect of personnel who might be introducing undue microbial hazards should be decided by a designated competent person.

10.5 Changing and washing should follow a written procedure designed to minimize the contamination of clean-area clothing or the carry-through of contaminants to clean areas. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.

10.6 Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilized or adequately sanitized) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least every working session. Operators working in grade A and B areas should wear sanitized goggles.

10.7 Wrist-watches, cosmetics and jewellery should not be worn in clean areas.

10.8 The clothing required for each grade is as follows:

- *Grade D.* The hair and, where relevant, beard and moustache should be covered. Protective clothing and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination from outside the clean area.
- *Grade C.* The hair and, where relevant, beard and moustache should be covered. A one-piece jumpsuit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes should be worn. The clothing should shed virtually no fibres or particulate matter.
- *Grades A and B.* Entry of personnel into grade A areas should be minimized. Headgear should totally enclose the hair and, where relevant, beard and moustache. A one-piece jumpsuit, gathered at the wrists and

with a high neck, should be worn. The headgear should be tucked into the neck of the suit. A facemask should be worn to prevent the shedding of droplets. Sterilized, non-powdered gloves of appropriate material and sterilized or disinfected footwear should be worn. Trouser-bottoms should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and should retain particles shed by the body.

10.9 Clothing used in clean areas should be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilization, there may be an increased risk of shedding particles. Washing and sterilization operations should follow standard operating procedures.

11. Premises

11.1 All premises should as far as possible be designed to avoid the unnecessary entry of supervisory or control personnel. Grade A and B areas should be designed so that all operations can be observed from outside.

11.2 In clean areas all exposed surfaces should be smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.

11.3 To reduce the accumulation of dust and to facilitate cleaning, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be carefully designed to avoid uncleanable recesses; sliding doors may be undesirable for this reason. Swing doors should open to the high-pressure side and be provided with self-closers. Exceptions are permitted based on egress and site environmental, health and safety containment requirements.

11.4 False ceilings should be sealed to prevent contamination from the void space above them.

11.5 Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Sanitary pipes and fittings should be used and threaded pipe connections should be avoided.

11.6 Sinks and drains should be avoided wherever possible and should be excluded from grade A and B areas where aseptic operations are carried out. Where installed they should be designed, located and maintained so as to minimize the risks of microbial contamination; they should be fitted with

effective, easily cleanable traps and with air breaks to prevent backflow. Any floor channels should be open and easily cleanable and be connected to drains outside the area in a manner that prevents the ingress of microbial contaminants.

11.7 Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand-washing facilities should be provided only in the first stage of the changing rooms.

There should not be a change of more than one grade between airlocks or passages and changing rooms, i.e. a grade D passage can lead to a grade C airlock, which leads to a grade B changing room, which leads to a grade B clean room. Changing rooms should be of a sufficient size to allow for ease of changing. Changing rooms should be equipped with mirrors so that personnel can confirm the correct fit of garments before leaving the changing room.

11.8 Airlock doors should not be opened simultaneously. An interlocking system and a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

11.9 A filtered air supply should be used to maintain a positive pressure and an airflow relative to surrounding areas of a lower grade under all operational conditions; it should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of approximately 10–15 Pascals (guidance value). Particular attention should be paid to the protection of the zone of greatest risk, i.e. the immediate environment to which the product and the cleaned components in contact with it are exposed. The recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain certain materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. The decontamination of the facilities and the treatment of air leaving a clean area may be necessary for some operations.

11.10 It should be demonstrated that airflow patterns do not present a contamination risk; for example, care should be taken to ensure that particles from a particle-generating person, operation or machine are not conveyed to a zone of higher product risk.

11.11 A warning system should be operated to indicate failure in the air supply. Indicators of pressure differentials should be fitted between areas

where this difference is important, and the pressure differentials should be regularly recorded and failure alarmed.

11.12 Consideration should be given to restricting unnecessary access to critical filling areas, e.g. grade A filling zones, by means of a physical barrier.

12. **Equipment**

12.1 A conveyor belt should not pass through a partition between a grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized (e.g. in a sterilizing tunnel).

12.2 Whenever possible, equipment used for processing sterile products should be chosen so that it can be effectively sterilized by steam or dry heat or other methods.

12.3 As far as possible, equipment fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance should be re-sterilized after complete reassembly, wherever possible.

12.4 When equipment maintenance is carried out within a clean area, clean instruments and tools should be used and the area should be cleaned and disinfected again, where appropriate, before processing recommences, if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work.

12.5 All equipment such as sterilizers, air-handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved.

12.6 Water-treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Consideration should be given to including a testing programme in the maintenance of a water system. Water for injection should be produced, stored and distributed in a manner which prevents the growth of microorganisms, e.g. by constant circulation at a temperature above 70°C or not more than 4°C (10).

13. **Finishing of sterile products**

13.1 Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules, should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

13.2 The container closure system for aseptically filled vials is not fully integral until the aluminum cap has been crimped into place on the stoppered vial. Crimping of the cap should, therefore, be performed as soon as possible after stopper insertion.

13.3 As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction.

13.4 Vial capping can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a grade A air supply until the cap has been crimped.

13.5 Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimize microbial contamination.

13.6 Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimizing direct human interventions into the capping operation.

13.7 Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, predetermined period.

13.8 Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is carried out visually this should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eyesight checks, using personal corrective lenses (e.g. spectacles or contact lenses) as required, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

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Annex 5

WHO good distribution practices for pharmaceutical products

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References

1. Introduction

Distribution is an important activity in the integrated supply-chain management of pharmaceutical products. Various people and entities are generally responsible for the handling, storage and distribution of such products. In some cases, however, a person or entity is only involved in and responsible for certain elements of the distribution process. The objective of these guidelines is to assist in ensuring the quality and identity of pharmaceutical products during all aspects of the distribution process. These aspects include, but are not limited to, procurement, purchasing, storage, distribution, transportation, repackaging, relabelling, documentation and record-keeping practices.

The storage, sale and distribution of pharmaceutical products are often carried out by various companies, institutions and individuals. This document sets out appropriate steps to assist in fulfilling the responsibilities involved in the different aspects of the distribution process within the supply chain and to avoid the introduction of counterfeits into the marketplace via the distribution chain. The relevant sections should be considered by various participants as applicable to the particular role that they play in the distribution of pharmaceutical products.

The nature of the risks involved is likely to be similar to that for risks encountered in the manufacturing environment, e.g. mix-ups, adulteration, contamination and cross-contamination. When the distribution chain is interrupted by manufacturing steps such as repackaging and relabelling, the principles of good manufacturing practices (GMP) should be applied to these processes.

Counterfeit pharmaceutical products are a real threat to public health and safety. Consequently, it is essential to protect the pharmaceutical supply chain against the penetration of such products. Weak points in the distribution processes of pharmaceutical products provide an avenue for counterfeit as well as illegally imported, stolen and substandard medicines to enter the supply chain. This is a concern in both developed and developing countries. The methods by which such products enter the supply chain have become increasingly complex and have resulted in the development of thriving secondary and grey markets throughout the world. The involvement of unauthorized entities in the distribution and sale of pharmaceutical products is a particular concern. Only a joint approach including all parties involved in the supply chain can be successful in the fight against counterfeit pharmaceutical products and, therefore, all parties active in the market should take an active part in collaborative activities.

Different models for the distribution of pharmaceutical products are used in different countries and sometimes within the same country, for example,

in the public and the private sector. These guidelines are intended to be applicable to all persons and outlets involved in any aspect of the distribution of pharmaceutical products from the premises of the manufacturer of the product to the person dispensing or providing pharmaceutical products directly to a patient or his or her agent. This includes all parties involved in trade and distribution of medicines, pharmaceutical manufacturers, including the manufacturers of finished products and pharmaceutical wholesalers as well as other parties such as brokers, suppliers, distributors, logistics providers, traders, transport companies and forwarding agents and their employees.

The relevant sections of these guidelines should also be considered for implementation by, among others, governments, regulatory bodies, international procurement organizations, donor agencies and certifying bodies, as well as all parties involved in any aspect of the trade and distribution of pharmaceutical products, including health care workers. The guidelines can also be used as a tool in the prevention of the distribution of counterfeit pharmaceutical products. It should, however, be noted that these are general guidelines which may be adapted to suit the prevailing situations and conditions in individual countries. National or regional guidelines may be developed to meet specific needs and situations in a particular region or country.

To maintain the original quality of pharmaceutical products, every party active in the distribution chain has to comply with the applicable legislation and regulations. Every activity in the distribution of pharmaceutical products should be carried out according to the principles of GMP, good storage practice (GSP) and good distribution practice (GDP) as applicable. These guidelines do not deal with all aspects of the standards for the storage of pharmaceuticals which are covered in the *WHO guide to good storage practices for pharmaceuticals* (1). The dispensing to patients is addressed in the WHO good pharmacy practice (GPP) guide (2). These guidelines should also be read in conjunction with other WHO guidelines (3–6).

2. **Scope of the document**

This document lays down guidelines for the distribution of pharmaceutical products. Depending on the national and regional legislation on pharmaceuticals, these guidelines may apply equally to products for human and for veterinary use. The guidelines thus cover products for which a prescription is required by the patient, products which may be provided to a patient without a prescription, biologicals and vaccines. Although medical devices are not included in the definition of pharmaceutical products for the purposes of this document, the main principles established in this document may also be used where applicable for medical devices.

The document does not specifically cover GMP aspects of finished products in bulk, distribution of labels or packaging, as these aspects are considered to be covered by other guidelines (3).

The principles for the distribution of starting materials (active pharmaceutical ingredients (APIs) and excipients) are also not covered here. These are laid down in the WHO guidance *Good trade and distribution practices for pharmaceutical starting materials* (7).

3. **Glossary**

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents.

agreement

Arrangement undertaken by and legally binding on parties.

auditing

An independent and objective activity designed to add value and improve an organization's operations by helping the organization to accomplish its objectives by using a systematic, disciplined approach to evaluate and improve the effectiveness of risk management, control and governance processes.

batch

A defined quantity of pharmaceutical products processed in a single process or series of processes so that it is expected to be homogeneous.

batch number

A distinctive combination of numbers and/or letters which uniquely identifies a batch, for example, on the labels, its batch records and corresponding certificates of analysis.

consignment

The quantity of pharmaceutical products supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include pharmaceutical products belonging to more than one batch.

container

The material employed in the packaging of a pharmaceutical product. Containers include primary, secondary and transportation containers.

Containers are referred to as primary if they are intended to be in direct contact with the product. Secondary containers are not intended to be in direct contact with the product.

contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material, intermediate or pharmaceutical product during handling, production, sampling, packaging or repackaging, storage or transportation.

contract

Business agreement for the supply of goods or performance of work at a specified price.

counterfeit pharmaceutical product

A pharmaceutical product which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products, and counterfeit pharmaceutical products may include products with the correct ingredients, with the wrong ingredients, without active ingredients, with an incorrect quantity of active ingredient or with fake packaging.

cross-contamination

Contamination of a starting material, intermediate product or finished pharmaceutical product with another starting material or product during production, storage and transportation.

distribution

The procuring, purchasing, holding, storing, selling, supplying, importing, exporting, or movement of pharmaceutical products, with the exception of the dispensing or providing pharmaceutical products directly to a patient or his or her agent.

expiry date

The date given on the individual container (usually on the label) of a pharmaceutical product up to and including the date on which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture.

first expiry/first out (FEFO)

A distribution procedure that ensures that the stock with the earliest expiry date is distributed and/or used before an identical stock item with a later expiry date is distributed and/or used.

forwarding agent

A person or entity engaged in providing, either directly or indirectly, any service concerned with clearing and forwarding operations in any manner to any other person and includes a consignment agent.

good distribution practices (GDP)

That part of quality assurance that ensures that the quality of a pharmaceutical product is maintained by means of adequate control of the numerous activities which occur during the distribution process as well as providing a tool to secure the distribution system from counterfeits, unapproved, illegally imported, stolen, counterfeit, substandard, adulterated, and/or misbranded pharmaceutical products.

good manufacturing practices (GMP)

That part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

good pharmacy practice (GPP)

The practice of pharmacy aimed at providing and promoting the best use of medicines and other health care services and products, by patients and members of the public. It requires that the welfare of the patient is the pharmacist's prime concern at all times.

good storage practices (GSP)

That part of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout the storage thereof.

good trade and distribution practices (GTDP)

That part of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout the numerous activities which occur during the trade and the distribution process.

importation

The act of bringing or causing any goods to be brought into a customs territory (national territory, excluding any free zone).

intermediate product

Partly processed product that must undergo further manufacturing steps before it becomes a bulk finished product.

labelling

Process of identifying a pharmaceutical product including the following information, as appropriate: name of the product; active ingredient(s),

type and amount; batch number; expiry date; special storage conditions or handling precautions; directions for use, warnings and precautions; names and addresses of the manufacturer and/or the supplier.

manufacture

All operations of purchase of materials and products, production, packaging, labelling, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

marketing authorization

A legal document issued by the competent medicines regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. It specifies the information on which authorization is based (e.g. “The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence”). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization.

Once a product has been given marketing authorization, it is included on a list of authorized products — the register — and is often said to be “registered” or to “have registration”. Market authorization may occasionally also be referred to as a “licence” or “product licence”.

pedigree

A complete record that traces the ownership of and transactions relating to a pharmaceutical product as it is distributed through the supply chain.

pharmaceutical product

Any product intended for human use, or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, which is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. It does not, however, include medical devices.

product recall

A process for withdrawing or removing a pharmaceutical product from the pharmaceutical distribution chain because of defects in the product, complaints of serious adverse reactions to the product and/or concerns

that the product is or may be counterfeit. The recall might be initiated by the manufacturer, importer, wholesaler, distributor or a responsible agency.

quality assurance

A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

quality system

An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product (or services) will satisfy given requirements for quality.

quarantine

The status of pharmaceutical products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

sampling

Operations designed to obtain a representative portion of a pharmaceutical product, based on an appropriate statistical procedure, for a defined purpose, e.g. acceptance of consignments or batch release.

shelf-life

The period of time during which a pharmaceutical product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

standard operating procedure (SOP)

An authorized, written procedure giving instructions for performing operations not necessarily specific to a given product but of a more general nature (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection).

storage

The storing of pharmaceutical products up to the point of use.

supplier

A person or entity engaged in the activity of providing products and/or services.

transit

The period during which pharmaceutical products are in the process of being carried, conveyed, or transported across, over or through a passage or route to reach the destination.

vehicles

Trucks, vans, buses, minibuses, cars, trailers, aircraft, railway carriages, boats and other means which are used to convey pharmaceutical products.

4. **General principles**

4.1 All parties involved in the distribution of pharmaceutical products have a responsibility to ensure that the quality of pharmaceutical products and the integrity of the distribution chain is maintained throughout the distribution process from the site of the manufacturer to the entity responsible for dispensing or providing the product to the patient or his or her agent.

4.2 The principles of GDP should be included in national legislation and guidelines for the distribution of pharmaceutical products, in a country or region as applicable, as a means of establishing minimum standards.

4.3 The principles of GDP are applicable both to pharmaceutical products moving forward in the distribution chain from the manufacturer to the entity responsible for dispensing or providing pharmaceutical products to the patient and to products which are moving backwards in the chain, for example, as a result of the return or recall thereof.

4.4 The principles of GDP should also be adhered to in the case of pharmaceutical products which are donated.

4.5 All entities involved in the distribution process should apply due diligence with adherence to the principles of GDP, for example, in procedures relating to traceability and in recognition of security risks.

4.6 There should be collaboration between all parties including governments, customs agencies, law enforcement agencies, regulatory authorities, manufacturers, distributors and entities responsible for the supply of pharmaceutical products to patients to ensure the quality and safety of pharmaceutical products and prevent the exposure of patients to counterfeit pharmaceutical products.

5. **Regulation of the distribution of pharmaceutical products**

5.1 National legislation should be in place to regulate the activities of persons or entities involved in the distribution of pharmaceutical products.

5.2 The distributor or the organization to which the distributor belongs should be an entity that is appropriately authorized in terms of applicable legislation to perform the function(s) that it intends to perform. The distributor or the organization to which it belongs should be held accountable for the activities that it performs which relate to the distribution of pharmaceutical products.

5.3 Only persons or entities which are authorized to do so and/or which hold the appropriate licence should be entitled to import or export pharmaceutical products.

5.4 Distributors or their agents may only distribute a pharmaceutical product within or to a country or territory if a marketing authorization or similar authorization has been granted, which allows the use of that pharmaceutical product in that country or territory.

5.5 Holders of an authorization to distribute pharmaceutical products should obtain their supplies of pharmaceutical products only from persons or entities which are in possession of the applicable authorization to sell or supply such products to a distributor.

5.6 Distributors or their agents should supply pharmaceutical products only to persons or entities which are themselves authorized to acquire such products either in terms of an authorization to act as a distributor or to sell or supply products directly to a patient or to his or her agent.

5.7 Some duties and responsibilities may be delegated or contracted out to suitably designated persons or entities as authorized and as necessary. Duties and responsibilities may only be delegated to entities which are suitably authorized in line with the national legislation. Duties and responsibilities should be specified in a written agreement. There should be no gaps or unexplained overlaps with regard to the application of GDP. These delegated and contracted out activities should be documented in agreements or contracts. There should be a periodic audit of such activities with regard to application of GDP.

5.8 If a distributor or his or her agent subcontracts an activity to another entity, the person or entity to whom the activity is subcontracted must be appropriately authorized to perform the subcontracted activity and should uphold the same standards as the distributor.

5.9 The sale of pharmaceutical products via the Internet should be limited to registered and authorized mail-order pharmacies or other authorized entities.

6. **Organization and management**

6.1 There should be an adequate organizational structure for each entity defined with the aid of an organizational chart. The responsibility, authority and interrelationships of all personnel should be clearly indicated.

6.2 Duties and responsibilities should be clearly defined and understood by the individuals concerned and recorded as written job descriptions. Certain activities may require special attention, such as the supervision of performance of activities, in accordance with local legislation. At every level of the supply chain, employees should be fully informed and trained in their duties and responsibilities.

6.3 A designated person should be appointed within the organization, who has defined authority and responsibility for ensuring that a quality system is implemented and maintained.

6.4 Managerial and technical personnel must have the authority and resources needed to carry out their duties and to set up and maintain a quality system, as well as to identify and correct deviations from the established quality system (see section 8).

6.5 The responsibilities placed on any one individual should not be so extensive as to present any risk to product quality.

6.6 There should be arrangements in place to ensure that management and personnel are not subject to commercial, political, financial and other pressures or conflict of interest that may have an adverse effect on the quality of service provided or on the integrity of pharmaceutical products.

6.7 Safety procedures relating to all relevant aspects including the safety of personnel and property, environmental protection and product integrity, should be in place.

7. Personnel

7.1 All personnel involved in distribution activities should be trained and qualified in the requirements of GDP, as applicable. Training should be based on written standard operating procedures (SOPs). Personnel should receive initial and continuing training relevant to their tasks, and be assessed as applicable, in accordance with a written training programme. In addition, training of the personnel should include the topic of product security, as well as aspects of product identification, the detection of counterfeits and the avoidance of counterfeits entering the supply chain. A record of all training, which includes details of subjects covered and participants trained, should be kept.

7.2 Key personnel involved in the distribution of pharmaceutical products should have the ability and experience appropriate to their responsibility for ensuring that pharmaceutical products are distributed properly.

7.3 There should be an adequate number of competent personnel involved in all stages of the distribution of pharmaceutical products in order to ensure that the quality of the product is maintained.

7.4 National regulations relating to the qualifications and experience of personnel should be adhered to.

7.5 Personnel dealing with hazardous pharmaceutical products (such as highly active materials, radioactive materials, narcotics, and other hazardous, environmentally sensitive and/or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fire or explosion) should be given specific training.

7.6 Personnel involved in the distribution of pharmaceutical products should wear garments suitable for the activities that they perform. Personnel dealing with hazardous pharmaceutical products, including products containing materials that are highly active, toxic, infectious or sensitizing, should be provided with protective garments as necessary.

7.7 Appropriate procedures relating to personnel hygiene, relevant to the activities to be carried out, should be established and observed. Such procedures should cover health, hygiene and clothing of personnel.

7.8 Procedures and conditions of employment for employees, including contract and temporary staff, and other personnel having access to pharmaceutical products must be designed and administered to assist in minimizing the possibility of such products coming into the possession of unauthorized persons or entities.

7.9 Codes of practice and punitive procedures should be in place to prevent and address situations where persons involved in the distribution of pharmaceutical products are suspected of, or found to be implicated in, any activities relating to the misappropriation, tampering, diversion or counterfeiting of any product.

8. Quality system

8.1 Within an organization, quality assurance serves as a management tool. There should be a documented quality policy describing the overall intentions and requirements of the distributor regarding quality, as formally expressed and authorized by management.

8.2 The quality system should include an appropriate organizational structure, procedure, processes and resources and systematic actions necessary to ensure adequate confidence that a product or service and its documentation will satisfy given requirements for quality. The totality of these actions is described as the quality system.

8.3 The quality system should include provisions to ensure that the holder of the marketing authorization, entity identified on the label (if different from the manufacturer), the appropriate national and/or international

regulatory bodies, as well as other relevant competent authorities, would be informed immediately in a case of confirmed or suspected counterfeiting of a pharmaceutical product. Such products should be stored in a secure, segregated area and clearly identified to prevent further distribution or sale.

8.4 Where electronic commerce (e-commerce) is used, i.e. electronic means are used for any of the distribution steps, defined procedures and adequate systems should be in place to ensure traceability and confidence in the quality of the pharmaceutical products concerned. Electronic transactions (including those conducted via the Internet), relating to the distribution of pharmaceutical products, should be performed only by authorized persons or entities.

8.5 Authorized procurement and release procedures for all administrative and technical operations performed should be in place to ensure that appropriate pharmaceutical products are sourced only from approved suppliers and distributed by approved entities. The approval should come from the competent authority of the individual country where the legal entity is registered.

8.6 Inspection, auditing and certification of compliance with a quality system (such as the applicable International Standardization Organization (ISO) series, or national or international guidelines) by external bodies is recommended. Such certification should not, however, be seen as a substitute for compliance with these GDP guidelines and the applicable principles of GMP relating to pharmaceutical products.

8.7 If measures to ensure the integrity of the pharmaceutical products in transit are in place, they should be managed properly. For example, if seal control programmes for transit shipment are used, numbers should be issued in a tracked and sequential manner, the integrity of seals should be monitored and numbers verified during transit and upon receipt. Written procedures should be in place for use in situations where pharmaceutical products are suspected of being or are found to be counterfeit.

8.8 Distributors should from time to time conduct risk assessments to assess potential risks to the quality and integrity of pharmaceutical products. The quality system should be developed and implemented to address any potential risks identified. The quality system should be reviewed and revised periodically to address new risks identified during a risk assessment.

Traceability of pharmaceutical products

8.9 Regulations should foster a safe, transparent and secure distribution system which includes product traceability throughout the supply chain. This is a shared responsibility among the parties involved. There should be

procedures in place to ensure document traceability of products received and distributed, to facilitate product recall.

8.10 All parties involved in the supply chain should be identifiable, depending on the type of product and on national policies and legislation.

8.11 Measures should be in place to ensure that pharmaceutical products have documentation that can be used to permit traceability of the products throughout distribution channels from the manufacturer/importer to the entity responsible for selling or supplying the product to the patient or his or her agent (see also 14.2). Records including expiry dates and batch numbers may be part of a secure distribution documentation enabling traceability.

8.12 Ideally there should be a procedure in place for the creation and maintenance of a pedigree for pharmaceutical products.

Provision should be made for a visual and/or analytical identification of potential counterfeit products. The procedure to be followed when a suspected product is identified should include provisions for notification, as appropriate, of the holder of the marketing authorization, entity identified on the label (if different from the manufacturer), the appropriate national and/or international regulatory bodies, as well as other relevant competent authorities (see also section 19).

8.13 A suitable and, to the extent possible, internationally compatible product coding, identification system should be in place and developed in collaboration with the various parties involved in the supply chain. While it is understood that a differentiated approach may be necessary for different products and regions, pedigree and/or track-and-trace technologies provide possible options to ensure traceability.

9. Premises, warehousing and storage

9.1 Good storage practices (GSP) are applicable in all circumstances where pharmaceutical products are stored and throughout the distribution process. For additional guidance relating to the general principles of storage of pharmaceutical products, refer to the *WHO guide to good storage practices for pharmaceuticals (1)*.

Storage areas

9.2 Precautions must be taken to prevent unauthorized persons from entering storage areas. Employees should comply with the company policies to maintain a safe, secure and efficient working environment.

9.3 Storage areas should be of sufficient capacity to allow the orderly storage of the various categories of pharmaceutical products, namely commercial

and non-commercial products, products in quarantine, and released, rejected, returned or recalled products as well as those suspected to be counterfeits.

9.4 Storage areas should be designed or adapted to ensure appropriate and good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Pharmaceutical products should be stored off the floor and suitably spaced to permit cleaning and inspection. Pallets should be kept in a good state of cleanliness and repair.

9.5 Storage areas should be clean and free from accumulated waste and vermin. Organizations in charge of distribution must ensure that premises and storage areas are cleaned regularly. There should also be a written programme for pest control. The pest control agents used should be safe and there should be no risk of contamination of pharmaceutical products. There should be appropriate procedures for the clean-up of any spillage to ensure complete removal of any risk of contamination.

9.6 If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination. Adequate cleaning procedures should be in place for the sampling areas.

9.7 Receiving and dispatch bays should protect pharmaceutical products from the weather. Receiving areas should be designed and equipped to allow incoming containers of pharmaceutical products to be cleaned, if necessary, before storage.

9.8 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and access restricted to authorized personnel. Any system replacing physical quarantine should provide equivalent security. For example, computerized systems can be used, provided that they are validated to demonstrate security of access.

9.9 Physical or other equivalent validated (e.g. electronic) segregation should be provided for the storage of rejected, expired, recalled or returned products and suspected counterfeits. The products and the areas concerned should be appropriately identified.

9.10 Unless there is an appropriate alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, recalled or suspected counterfeit pharmaceutical products, separate storage areas should be assigned for their temporary storage until a decision as to their future has been made.

9.11 Radioactive materials, narcotics and other hazardous, sensitive and/or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fire or explosion (e.g. combustible or flammable liquids and solids and pressurized gases) should be stored in a dedicated area(s) that is subject to appropriate additional safety and security measures.

9.12 Pharmaceutical products should be handled and stored in such a manner as to prevent contamination, mix-ups and cross-contamination.

9.13 A system should be in place to ensure that the pharmaceutical products due to expire first are sold and/or distributed first (first expiry/first out (FEFO)). Exceptions may be permitted as appropriate, provided that adequate controls are in place to prevent the distribution of expired products.

9.14 Broken or damaged items should be withdrawn from usable stock and stored separately.

9.15 Storage areas should be provided with adequate lighting to enable all operations to be carried out accurately and safely.

Storage conditions and stock control

9.16 Storage and handling conditions should comply with applicable national and local regulations (8).

9.17 Storage conditions for pharmaceutical products should be in compliance with the recommendations of the manufacturer.

9.18 Facilities should be available for the storage of all pharmaceutical products under appropriate conditions (e.g. environmentally controlled when necessary). Records should be maintained of these conditions if they are critical for the maintenance of the characteristics of the pharmaceutical product stored.

9.19 Records of temperature monitoring data should be available for review. There should be defined intervals for checking temperature. The equipment used for monitoring should be checked at suitable predetermined intervals and the results of such checks should be recorded and retained. All monitoring records should be kept for at least the shelf-life of the stored pharmaceutical product plus one year, or as required by national legislation. Temperature mapping should show uniformity of the temperature across the storage facility. It is recommended that temperature monitors be located in areas that are most likely to show fluctuations.

9.20 Equipment used for monitoring of storage conditions should also be calibrated at defined intervals.

9.21 Periodic stock reconciliation should be performed by comparing the actual and recorded stocks. This should be done at defined intervals.

9.22 Stock discrepancies should be investigated in accordance with a specified procedure to check that there have been no inadvertent mix-ups, incorrect issues and receipts, thefts and/or misappropriations of

pharmaceutical products. Documentation relating to the investigation should be kept for a predetermined period.

10. **Vehicles and equipment**

10.1 Vehicles and equipment used to distribute, store or handle pharmaceutical products should be suitable for their purpose and appropriately equipped to prevent exposure of the products to conditions that could affect their stability and packaging integrity, and to prevent contamination of any kind.

10.2 The design and use of vehicles and equipment must aim to minimize the risk of errors and permit effective cleaning and/or maintenance to avoid contamination, build-up of dust or dirt and/or any adverse effect on the quality of the pharmaceutical products being distributed.

10.3 Where feasible, consideration should be given to adding technology, such as global positioning system (GPS) electronic tracking devices and engine-kill buttons to vehicles, which would enhance the security of pharmaceutical products while in the vehicle.

10.4 Dedicated vehicles and equipment should be used, where possible, when handling pharmaceutical products.

10.5 Where non-dedicated vehicles and equipment are used, procedures should be in place to ensure that the quality of the pharmaceutical product will not be compromised. Appropriate cleaning should be performed, checked and recorded.

10.6 Procedures should be in place to ensure that the integrity of the products is not compromised during transportation.

10.7 Where third-party carriers are used, distributors should develop written agreements with carriers to ensure that appropriate measures are taken to safeguard pharmaceutical products, including maintaining appropriate documentation and records. Such agreements should be in line with national and regional regulatory requirements.

10.8 Defective vehicles and equipment should not be used and should either be labelled as such or removed from service.

10.9 There should be procedures in place for the operation and maintenance of all vehicles and equipment involved in the distribution process, including cleaning and safety precautions.

10.10 Vehicles, containers and equipment should be kept clean and dry and free from accumulated waste. Organizations in charge of distribution must ensure that vehicles used are cleaned regularly.

10.11 Vehicles, containers and equipment should be kept free from rodents, vermin, birds and other pests. There should be written programmes and records for such pest control. The cleaning and fumigation agents used should not have any adverse effect on product quality.

10.12 Equipment chosen and used for the cleaning of vehicles should not constitute a source of contamination. Agents used for the cleaning of vehicles should be approved by management.

10.13 Special attention should be paid to the design, use, cleaning and maintenance of all equipment used for the handling of pharmaceutical products which are not in a protective shipping carton or case.

10.14 Where special storage conditions (e.g. temperature and/or relative humidity), different from, or limiting, the expected environmental conditions, are required during transportation, these should be provided, checked, monitored and recorded. All monitoring records should be kept for a minimum of the shelf-life of the product distributed plus one year, or as required by national legislation. Records of monitoring data should be made available for inspection by the regulatory or other oversight body.

10.15 Equipment used for monitoring conditions, e.g. temperature and humidity, within vehicles and containers should be calibrated at regular intervals.

10.16 Vehicles and containers should be of sufficient capacity to allow orderly storage of the various categories of pharmaceutical products during transportation.

10.17 Where possible, mechanisms should be available to allow for the segregation during transit of rejected, recalled and returned pharmaceutical products as well as those suspected of being counterfeits. Such goods should be securely packaged, clearly labelled, and be accompanied by appropriate supporting documentation.

10.18 Measures should be in place to prevent unauthorized persons from entering and/or tampering with vehicles and/or equipment, as well as to prevent the theft or misappropriation thereof.

11. Shipment containers and container labelling

11.1 Pharmaceutical products should be stored and distributed in shipment containers that have no adverse effect on the quality of the products, and that offer adequate protection from external influences, including contamination.

11.2 Shipping containers should bear labels providing sufficient information on handling and storage conditions and precautions to ensure

that the products are properly handled and secure at all times. The shipment container should enable identification of the container's contents and source.

11.3 The need for any special transport and/or storage conditions should be stated on the shipment container label. If a pharmaceutical product is intended for transfer to areas outside the control of the manufacturer's products management system, the name and address of the manufacturer, special transport conditions and any special legal requirements, including safety symbols, should also be included on the container label.

11.4 Normally, internationally and/or nationally accepted abbreviations, names or codes should be used in the labelling of shipment containers.

11.5 Special care should be taken when using dry ice in shipment containers. In addition to safety issues it must be ensured that the pharmaceutical product does not come into contact with the dry ice, as it may have an adverse effect on the quality of the product.

11.6 Written procedures should be available for the handling of damaged and/or broken shipment containers. Particular attention should be paid to those containing potentially toxic and hazardous products.

12. Dispatch and receipt

12.1 Pharmaceutical products should only be sold and/or distributed to persons or entities that are authorized to acquire such products in accordance with the applicable national, regional and international legislation. Written proof of such authority must be obtained prior to the distribution of products to such persons or entities.

12.2 Prior to the dispatch of the pharmaceutical products, the supplier should ensure that the person or entity, e.g. the contract acceptor for transportation of the pharmaceutical products, is aware of the pharmaceutical products to be distributed and complies with the appropriate storage and transport conditions.

12.3 The dispatch and transportation of pharmaceutical products should be undertaken only after the receipt of a valid delivery order or material replenishment plan, which should be documented.

12.4 Written procedures for the dispatch of pharmaceutical products should be established. Such procedures should take into account the nature of the product as well as any special precautions to be observed. Pharmaceutical products under quarantine will require release for dispatch by the person responsible for quality (see 6.3).

12.5 Records for the dispatch of pharmaceutical products should be prepared and should include at least the following information:

- date of dispatch;
- complete business name and address (no acronyms), type of entity responsible for the transportation, telephone number and names of contact persons;
- complete business name, address (no acronyms), and status of the addressee (e.g. retail pharmacy, hospital or community clinic);
- a description of the products including, e.g. name, dosage form and strength (if applicable);
- quantity of the products, i.e. number of containers and quantity per container (if applicable);
- applicable transport and storage conditions;
- a unique number to allow identification of the delivery order; and
- assigned batch number and expiry date (where not possible at dispatch, this information should at least be kept at receipt to facilitate traceability).

12.6 Records of dispatch should contain enough information to enable traceability of the pharmaceutical product. Such records should facilitate the recall of a batch of a product, if necessary, as well as the investigation of counterfeit or potentially counterfeit pharmaceutical products.

12.7 In addition, the assigned batch number and expiry date of pharmaceutical products should be recorded at the point of receipt to facilitate traceability.

12.8 Methods of transportation, including vehicles to be used, should be selected with care, and local conditions should be considered, including the climate and any seasonal variations experienced. Delivery of products requiring controlled temperatures should be in accordance with the applicable storage and transport conditions.

12.9 Delivery schedules should be established and routes planned, taking local needs and conditions into account. Such schedules and plans should be realistic and systematic. Security risks should also be taken into account when planning the schedules and routes of the delivery.

12.10 Care should be taken to ensure that the volume of pharmaceutical products ordered does not exceed the capacity of storage facilities at the destination.

12.11 Vehicles and containers should be loaded carefully and systematically, where applicable on a first-out/last-in basis, to save time when unloading, prevent physical damage and reduce security risks. Extra care should be taken during loading and unloading of cartons to avoid damage.

12.12 Pharmaceutical products should not be supplied or received after their expiry date, or so close to the expiry date that this date is likely to be reached before the products are used by the consumer.

12.13 Incoming shipments should be examined to verify the integrity of the container/closure system, ensure that tamper-evident packaging features are intact, and that labelling appears intact.

13. **Transportation and products in transit**

13.1 Products and shipment containers should be secured to prevent or provide evidence of unauthorized access. Vehicles and operators should be provided with additional security, as appropriate, to prevent theft and other misappropriation of products during transportation.

13.2 Product shipments should be secured and include the appropriate documentation to facilitate identification and verification of compliance with regulatory requirements. Policies and procedures should be followed by all persons involved in the transportation, to secure pharmaceutical products.

13.3 The people responsible for the transportation of pharmaceutical products should be informed about all relevant conditions for storage and transportation. These requirements should be adhered to throughout transportation and at any intermediate storage stages.

13.4 Pharmaceutical products should be stored and transported in accordance with procedures such that:

- The identity of the product is not lost.
- The product does not contaminate and is not contaminated by other products.
- Adequate precautions are taken against spillage, breakage, misappropriation and theft.
- Appropriate environmental conditions are maintained, e.g. using cold chain for thermolabile products.

13.5 The required storage conditions for pharmaceutical products should be maintained within acceptable limits during transportation. If a deviation has been noticed during transportation by the person or entity responsible for transportation, this should be reported to the distributor and recipient. In cases where the recipient notices the deviation, it should be reported to the distributor. Where necessary, the manufacturer of the pharmaceutical product should be contacted for information about appropriate steps to be taken.

13.6 Where special conditions are required during transportation that are different from or limit the given environmental conditions (e.g. temperature and humidity) these should be provided by the manufacturer on the labels, monitored and recorded.

13.7 Written procedures should be in place for investigating and dealing with any failure to comply with storage requirements, e.g. temperature deviations.

13.8 Transportation and storage of pharmaceutical products containing hazardous substances, such as toxic, radioactive material, and other dangerous pharmaceutical products presenting special risks of abuse, fire or explosion (e.g. combustible or flammable liquids, solids and pressurized gases) should be stored in safe, dedicated and secure areas, and transported in safe, suitably designed, secured containers and vehicles. In addition, the requirements of applicable international agreements and national legislation should be met.

13.9 Products containing narcotics and other dependence-producing substances should be transported in safe and secure containers and vehicles and be stored in safe and secure areas.

In addition, applicable international agreements and national legislation should be complied with.

13.10 Spillages should be cleaned up as soon as possible to prevent possible contamination, cross-contamination and hazards. Written procedures should be in place for the handling of such occurrences.

13.11 Physical or other equivalent (e.g. electronic) segregation should be provided for the storage and distribution during transit of rejected, expired, recalled or returned pharmaceutical products and suspected counterfeits. The products should be appropriately identified, securely packaged, clearly labelled and be accompanied by appropriate supporting documentation.

13.12 The interiors of vehicles and containers should remain clean and dry while pharmaceutical products are in transit.

13.13 Packaging materials and shipment containers should be of suitable design to prevent damage of pharmaceutical products during transport. Seal control programmes should be in place and managed properly.

13.14 Drivers of vehicles should identify themselves and present appropriate documentation to demonstrate that they are authorized to transport the load.

13.15 Damage to containers and any other event or problem that occurs during transit must be recorded and reported to the relevant department, entity or authority, and investigated.

13.16 Pharmaceutical products in transit must be accompanied by the appropriate documentation.

14. Documentation

14.1 Written instructions and records which document all activities relating to the distribution of pharmaceutical products, including all applicable receipts and issues (invoices) should be available. Records should be kept for seven years, unless otherwise specified in national or regional regulations.

14.2 Distributors should keep records of all pharmaceutical products received. Records should contain at least the following information:

- date;
- name of the pharmaceutical product;
- quantity received, or supplied; and
- name and address of the supplier.

14.3 Procedures should be established and maintained for the preparation, review, approval, use of and control of changes to all documents relating to the distribution process. Procedures must be in place for both internally generated documents and those from external sources.

14.4 Documents, and in particular instructions and procedures relating to any activity that could have an impact on the quality of pharmaceutical products, should be designed, completed, reviewed and distributed with care.

14.5 The title, nature and purpose of each document should be clearly stated. The contents of documents should be clear and unambiguous. Documents should be laid out in an orderly fashion and be easy to check.

14.6 All documents should be completed, approved, signed (as required) and dated by an appropriate authorized person(s) and should not be changed without the necessary authorization.

14.7 The nature, content and retention of documentation relating to the distribution of pharmaceutical products and any investigations conducted and action taken, should comply with national legislative requirements. Where such requirements are not in place, the documents should be retained for at least one year after the expiry date of the product concerned.

14.8 The distributor must establish and maintain procedures for the identification, collection, indexing, retrieval, storage, maintenance, disposal of and access to all applicable documentation.

14.9 All records must be readily retrievable, and be stored and retained using facilities that are safeguarded against unauthorized modification, damage, deterioration and/or loss of documentation.

14.10 Documents should be reviewed regularly and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.

14.11 Mechanisms should exist to allow for transfer of information, including quality or regulatory information, between a manufacturer and a customer, as well as the transfer of information to the relevant regulatory authority as required.

14.12 Records relating to storage of pharmaceutical products should be kept and be readily available upon request in accordance with the *WHO guidelines on good storage practice for pharmaceuticals (I)*.

14.13 Permanent records, written or electronic, should exist for each stored product indicating recommended storage conditions, any precautions to be observed and retest dates. Pharmacopoeial requirements and current national regulations concerning labels and containers should be respected at all times.

14.14 Procedures should be in place for temperature mapping, security services to prevent theft or tampering with goods at the storage facilities, destruction of unsaleable or unusable stocks and on retention of the records.

14.15 Where the records are generated and kept in electronic form, back ups should be maintained to prevent any accidental data loss.

15. **Repackaging and relabelling**

15.1 Repackaging and relabelling of pharmaceutical products should be limited, as these practices may represent a risk to the safety and security of the supply chain.

15.2 Where they do occur, they should only be performed by entities appropriately authorized to do so and in compliance with the applicable national, regional and international guidelines, i.e. in accordance with GMP principles.

15.3 In the event of repackaging by companies other than the original manufacturer, these operations should result in at least equivalent means of identification and authentication of the products.

15.4 Procedures should be in place for the secure disposal of original packaging.

16. **Complaints**

16.1 There should be a written procedure in place for the handling of complaints. A distinction should be made between complaints about a product or its packaging and those relating to distribution. In the case of a complaint about the quality of a product or its packaging, the original manufacturer and/or marketing authorization holder should be informed as soon as possible.

16.2 All complaints and other information concerning potentially defective and potentially counterfeit pharmaceutical products should be reviewed carefully according to written procedures describing the action to be taken, including the need to consider a recall where appropriate.

16.3 Any complaint concerning a material defect should be recorded and thoroughly investigated to identify the origin or reason for the complaint (e.g. repackaging procedure or original manufacturing process).

16.4 If a defect relating to a pharmaceutical product is discovered or suspected, consideration should be given to whether other batches of the product should also be checked.

16.5 Where necessary, appropriate follow-up action should be taken after investigation and evaluation of the complaint. There should be a system in place to ensure that the complaint, the response received from the original product manufacturer, or the results of the investigation of the complaint, are shared with all the relevant parties.

16.6 Product quality problems or suspected cases of counterfeit products should be documented and the information shared with the appropriate national and/or regional regulatory authorities.

17. **Recalls**

17.1 There should be a system, which includes a written procedure, to effectively and promptly recall pharmaceutical products known or suspected to be defective or counterfeit, with a designated person(s) responsible for recalls. The system should comply with the guidance issued by the national or regional regulatory authority. This procedure should be checked regularly and updated as necessary.

17.2 The original manufacturer and/or marketing authorization holder should be informed in the event of a recall. Where a recall is instituted by an entity other than the original manufacturer and/or marketing authorization holder, consultation with the original manufacturer and/or marketing authorization holder should, where possible, take place before the recall is instituted.

Information on a recall should be shared with the appropriate national or regional regulatory authority. If a recall of the original product is necessary because of a counterfeited product which is not easily distinguishable from the original product, the manufacturer of the original product and the relevant health authority should be informed.

17.3 The effectiveness of the arrangements for recalls should be evaluated at regular intervals. All recalled pharmaceutical products should be stored in a secure, segregated area pending appropriate action.

17.4 Recalled pharmaceutical products should be segregated during transit and clearly labelled as recalled products. Where segregation in transit is not possible, such goods must be securely packaged, clearly labelled, and be accompanied by appropriate documentation.

17.5 The particular storage conditions applicable to a pharmaceutical product which is subject to recall should be maintained during storage and transit until such time as a decision has been made regarding the fate of the product in question.

17.6 All customers and competent authorities of all countries to which a given pharmaceutical product may have been distributed should be informed promptly of any intention to recall the product because it is, or is suspected to be, defective or counterfeit.

17.7 All records should be readily available to the designated person(s) responsible for recalls. These records should contain sufficient information on pharmaceutical products supplied to customers (including exported products).

17.8 The progress of a recall process should be recorded and a final report issued, which includes a reconciliation between delivered and recovered quantities of products.

17.9 When necessary emergency recall procedures should be implemented.

18. **Returned products**

18.1 A distributor should receive pharmaceutical product returns or exchanges pursuant to the terms and conditions of the agreement between the distributor and the recipient. Both distributors and recipients should be accountable for administering their returns process and ensuring that the aspects of this operation are secure and do not permit the entry of counterfeit products.

18.2 The necessary assessment and decision regarding the disposition of such products must be made by a suitably authorized person. The nature of the product returned to the distributor, any special storage conditions required, its condition and history and the time elapsed since it was issued, should all be taken into account in this assessment. Where any doubt arises over the quality of a pharmaceutical product, it should not be considered suitable for reissue or reuse

18.3 Provision should be made for the appropriate and safe transport of returned products in accordance with the relevant storage and other requirements.

18.4 Rejected pharmaceutical products and those returned to a distributor should be appropriately identified and handled in accordance with a procedure which involves at least:

- the physical segregation of such pharmaceutical products in quarantine in a dedicated area; or
- other equivalent (e.g. electronic) segregation.

This is to avoid confusion and prevent distribution until a decision has been taken with regard to their disposition. The particular storage conditions applicable to a pharmaceutical product which is rejected or returned should be maintained during storage and transit until such time as a decision has been made regarding the product in question.

18.5 Provision should be made for the appropriate and safe transport of rejected pharmaceutical products prior to their disposal.

18.6 Destruction of pharmaceutical products should be done in accordance with international, national and local requirements regarding disposal of such products, and with due consideration to protection of the environment.

18.7 Records of all returned, rejected and/or destroyed pharmaceutical products should be kept for a predetermined period.

19. **Counterfeit pharmaceutical products**

19.1 Counterfeit pharmaceutical products found in the distribution chain should be kept apart from other pharmaceutical products to avoid any confusion. They should be clearly labelled as not for sale and national regulatory authorities and the holder of the marketing authorization for the original product should be informed immediately.

19.2 The sale and distribution of a suspected counterfeit pharmaceutical product should be suspended and the national regulatory authority notified without delay.

19.3 Upon confirmation of the product being counterfeit a formal decision should be taken on its disposal, ensuring that it does not re-enter the market, and the decision recorded.

20. **Importation**

20.1 Consideration should be given to the *WHO guidelines on import procedures for pharmaceutical products (6)*. The following aspects should be given particular attention.

20.2 The number of ports of entry in a country for the handling of imports of pharmaceutical products should be limited by appropriate legislation. Such ports could be designated by the state.

20.3 The chosen port(s) of entry should be those most appropriately located and best equipped to handle imports of pharmaceutical products.

20.4 At the port of entry, consignments of pharmaceutical products should be stored under suitable conditions for as short a time as possible.

20.5 All reasonable steps should be taken by importers to ensure that products are not mishandled or exposed to adverse storage conditions at wharves or airports.

20.6 Where necessary, persons with pharmaceutical training should be involved with the customs procedures or should be readily contactable.

20.7 The *WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce* should be used to provide data regarding quality assessment of imported pharmaceutical products.

20.8 Customs, enforcement agencies and regulatory agencies responsible for supervision of pharmaceutical products should establish means for cooperation and information exchange in order to prevent importation of counterfeit pharmaceutical products.

21. **Contract activities**

21.1 Any activity relating to the distribution of a pharmaceutical product which is delegated to another person or entity should be performed by parties appropriately authorized for that function and in accordance with the terms of a written contract.

21.2 The contract should define the responsibilities of each party including observance of the principles of GDP and relevant warranty clauses. It should also include responsibilities of the contractor for measures to avoid the entry of counterfeit medicines into the distribution chain, such as by suitable training programmes.

21.3 All contract accepters should comply with the requirements in these guidelines.

21.4 Subcontracting may be permissible, under certain conditions and subject to the written approval of the contract giver; however, the subcontractors should be authorized for the function.

21.5 Contract accepters should be audited periodically.

22. **Self-inspection**

22.1 The quality system should include self-inspections. These should be conducted to monitor implementation and compliance with the principles of GDP and, if necessary, to trigger corrective and preventive measures.

22.2 Self-inspections should be conducted in an independent and detailed way by a designated, competent person.

22.3 The results of all self-inspections should be recorded. Reports should contain all observations made during the inspection and, where applicable, proposals for corrective measures. There should be an effective follow-up programme. Management should evaluate the inspection report and the records of any corrective actions taken.

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3. WHO good manufacturing practices. In: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Good manufacturing practices and inspection, Vol. 2*, 2nd updated ed. Geneva, World Health Organization, 2007.
4. Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 10 (WHO Technical Report Series, No. 863).
5. WHO pharmaceutical starting materials certification scheme (SMACS). In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2004, Annex 3 (Technical Report Series, No. 917).
6. Guidelines on import procedures for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 12 (WHO Technical Report Series, No. 863).
7. Good trade and distribution practices for pharmaceutical starting materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2004, Annex 2 (WHO Technical Report Series, No. 917).
8. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 2 (WHO Technical Report Series, No. 953) (http://www.who.int/medicines/areas/quality_safety/quality_assurance/regulatory_standards/en/index.html).

Annex 6

Guidelines on the requalification of prequalified dossiers

1. Introduction
2. Requalification of prequalified dossiers

Appendix 1
Summary of key product information

Appendix 2
Variations to the product

1. Introduction

In accordance with the provisions set out in section 12 (Maintenance of prequalification status) of the *Procedure for prequalification of pharmaceutical products*¹, holders of WHO-prequalified products should submit a quality review 5 years from the date of prequalification of the product, or when requested to do so by WHO Prequalification (whichever date is earlier).

Section 12 of the above-mentioned guidelines states that:

WHO will furthermore arrange for the products and manufacturing sites included in the list to be re-evaluated at regular intervals. If, as a result of this re-evaluation, it is found that a product and/or specified manufacturing site no longer complies with the WHO-recommended standards, such products and manufacturing sites will be removed from the list. Failure of a manufacturer or applicant to participate in the re-evaluation procedure will also lead to removal from the list.

Re-evaluation, including re-inspections of manufacturing sites and contract research organizations (CROs), will be done at regular intervals, based on risk assessment, but at least once every 5 years.

Re-evaluation, including re-inspections, shall also be performed:

¹ Procedure for prequalification of pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 4 (WHO Technical Report Series, No. 953) (http://www.who.int/medicines/publications/pharmprep/pdf_trs953.pdf#page=145).

- if any fraud or omissions by the applicant, manufacturer(s) of a finished pharmaceutical product (FPP) or active pharmaceutical ingredient (API), or CROs in the initial assessment procedure or during the follow-up activities, becomes evident; and
- if WHO or any United Nations agency considers that a batch or batches of supplied prequalified pharmaceutical products are not in compliance with the specifications which were found to be applicable upon prequalification.

Requalification will be applicable to multisource FPPs (generics) where the full dossiers have been submitted, assessed and prequalified by WHO. Renewal of marketing authorization for products that have been listed by WHO based on approval by a stringent regulatory agency² (SRA) remains the responsibility of the relevant SRA.

2. **Requalification of prequalified dossiers**

The objective of this quality review submission is to enable WHO to requalify the product based on an assessment of the data and information submitted by the holder of a prequalified product, which includes verification of the acceptability of the product and its conformity to current norms and standards, and assessment of consistency of the quality of the prequalified FPPs, and its manufacturing process(es) over the identified period.

The holder of a prequalified product should submit the following documents electronically (in pdf format and in also in WinWord where indicated):

- A covering letter, which should contain a clear statement by the responsible person submitting the quality review, indicating that the information submitted is true and correct.
- Summary of key product information (as per Appendix 1).
- Variations to the product (as per Appendix 2).
- A pharmaceutical quality information form (PQIF)³, completed in WinWord format. It should reflect the requirements of current prequalification guidelines and should also take into account technical and

² Stringent regulatory authority (SRA): a regulatory authority which is:
a member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org);
or

an ICH observer, being the European Free Trade Association (EFTA), as represented by Swiss Medic, Health Canada and World Health Organization (WHO) (as may be updated from time to time); or
a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

³ Presentation of pharmaceutical quality information. In: *Guidance for submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*. Annex 8 (http://apps.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc).

scientific progress. The API and FPP specifications should be provided in tabulated format, comparing the specifications at prequalification and at the time of the requalification submission.

- Copies of the current API and FPP specifications, duly signed and dated, including the test methods. The specifications should indicate the reference number, version number, effective date and change history if any.

A product quality review may be submitted as supportive documentation. It may also be requested by WHO.

Appendix 1

Summary of key product information

This section compares key information on the FPP at the time of prequalification and at the time of the submission for requalification. Table A1.1 should be completed by the holder of the prequalified product. Include remarks as a footnote to Table A1.1, where deemed necessary, to clarify the information provided.

Table A1.1

Summary of key product information

Item	Prequalified dossier	Current data ^a
Product number (e.g. HA001)		
INN, strength and pharmaceutical form		
Applicant (name, physical address and contact numbers)		
Manufacturing site(s) of FPP, with physical address (including unit and block numbers) and contact numbers (list separately if different steps are performed by different sites, e.g. packaging, quality control)		
Batch size(s) of FPP		
Product description (visual appearance)		
Primary and secondary packaging material(s) and pack size(s)		
Storage conditions of FPP		
Shelf-life of FPP		
FPP specification(s) reference number and/or version ^b		
Manufacturer(s) of API(s), with physical address (including unit and block numbers) and contact numbers (list each API separately)		
Number/version of each APIMF associated with the FPP		
Storage conditions of API		
Retest period of API(s)		
API specification(s) reference number and/or version (for each API) ^b		
All commitments and their outcomes		

INN, international nonproprietary name; FPP, finished pharmaceutical product; API, active pharmaceutical ingredient; APIMF, active pharmaceutical ingredient master file.

^a If there has been no update of the dossier then indicate "N/A" (not applicable).

^b According to the latest editions of *The International Pharmacopoeia* (Ph.Int.), the European Pharmacopoeia (Ph.Eur), the British Pharmacopoeia (BP) and/or the United States Pharmacopoeia (USP). Where in-house specifications have been approved and there is now a monograph in any of the internationally-recognized pharmacopoeias (Ph.Int., Ph.Eur, BP, or USP), the specifications should be updated to comply with the new monograph or demonstrated to be at least equivalent. In the case that no compendial monograph exists, the applicant should ensure that the approved in-house specifications are updated, through the variation process, to reflect the requirements of current prequalification guidelines and to take into account technical and scientific progress (e.g. current ICH guidelines, general chapters of the Ph.Int.). Each new version of the documents should allow traceability to the prequalified dossier and approved variations.

Appendix 2

Variations to the product

The holder of the prequalified product should submit a review, in tabular format, of any minor and/or major changes (including those pending) to the initially prequalified product or to the terms of the initially prequalified dossier. Table A2.1 should be completed by the holder of the prequalified product.

Table A2.1

Information on variations to the prequalified product

Reference no.	Date of submission	Date of approval/ rejection and reference number of the letter	Date of implementation
Major changes			
Description of the change, e.g. change in the primary packaging site of a sterile product			
Minor changes			
Description of the change according to the PQ variation guide			

Add as many rows as necessary.

Note. Requests for variations should have been submitted in accordance with WHO's Guidance on variations to a prequalified product dossier⁴.

⁴ WHO Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007, Annex 6 (WHO Technical Report Series, No. 943) (http://apps.who.int/prequal/info_general/documents/TRS943/TRS943.pdf#page=121).

Annex 7

Guidelines for the preparation of a contract research organization master file

Background

1. General information
2. Quality management system of the contract research organization
3. Personnel
4. Ethics committee
5. Computer systems
6. Equipment and instruments
7. Documentation
8. Safety monitoring
9. Investigational medicinal products and comparator products
10. Pathology
11. Bioanalytical laboratory
12. Biostatistics
13. Study volunteers
14. Other information

Background

A contract research organization master file (CROMF) is a document prepared by the contract research organization (CRO) containing specific and factual information about the CRO and the conduct of clinical studies as well as the analyses of samples and related operations (including clinical trials, clinical data management, pharmacokinetics and statistical analysis and regulatory affairs) carried out at the named site. If only some of the operations referred to below are carried out at the site, the master file (MF) needs to be presented only for those operations.

In a case where a CRO is responsible for activities pertaining only to bioanalytical procedures, then only sections in the CROMF relating to these should be described. Other sections may be marked as “not applicable”.

Where a CRO performs various activities, separate sections could be prepared for the different units, e.g. clinical pharmacology unit (CPU) and bioanalytical laboratory (BAL).

A CROMF provides information on the policies, approach and general activities of a CRO. It is not trial-specific as trial-specific data are submitted in a product dossier. It serves as general information to regulators and can be used during preparation for inspections by regulatory inspectors in addition to the trial-specific data and information submitted for assessment. It also provides an overview of the organization’s approach to good clinical practices (GCP), good laboratory practices (GLP) and other guidelines pertaining to its activities.

A CROMF should be submitted to the national medicines regulatory authority (NMRA) where such a document is requested. It should be succinct and as far as possible not exceed 25 A4 pages (where appropriate, supportive documentation may be appended).

An updated CROMF should be submitted when requested by the NMRA, or if significant changes have been implemented by the CRO.

1. General information

- 1.1 Name and exact address of the CRO, including telephone, fax, 24-hour telephone numbers and e-mail address
- 1.2 Short description of the CRO (including size, location, number of beds, layout and plan, areas for handling samples and waste)
- 1.3 Activities as licensed/authorized by the national authority
- 1.4 Inspections and approvals

- 1.4.1 Inspections/approvals/accreditations by any regulatory agency
- 1.4.2 Audits of subcontractors
- 1.5 Type of studies (and indications, where appropriate) performed on site (a list of projects conducted at this site may be provided)
- 1.6 Provisions for insurance
 - 1.6.1 Number of employees engaged in studies, quality, storage and distribution
- 1.7 Contract services employed
 - 1.7.1 Use of outside scientific, analytical or other technical assistance in relation to studies and analysis (e.g. clinical laboratory, bioanalytical laboratory, X-ray facilities and caterers)
 - 1.7.2 Services outsourced, e.g. contracts with tertiary care hospital for handling of medical emergencies, ambulance facility, nutrition, biomedical waste, chemical waste, caterers, pest control and pathology laboratory

2. **Quality management system of the contract research organization**

(Short description including, e.g. responsibilities of the quality assurance unit. A list of quality system documents can be included)

- 2.1 Organization chart including the arrangements for quality assurance
- 2.2 Internal audits and self inspection
- 2.3 Corrective and preventive action plans (CAPA)

3. **Personnel**

(A brief description can be presented in tabular format)

- 3.1 Qualifications, experience and responsibilities of key personnel as applicable
 - 3.1.1 project manager
 - 3.1.2 principal investigator
 - 3.1.3 analytical investigator
 - 3.1.4 biostatistician
 - 3.1.5 clinical research associates
 - 3.1.6 data manager

- 3.1.7 monitor
- 3.1.8 the study director(s)
- 3.1.9 person responsible for quality assurance
- 3.2 Training of personnel:
 - 3.2.1 training policy and procedure (brief description)
 - 3.2.2 training records

4. **Ethics committee**

- 4.1 Constitution and relation to CRO
- 4.2 Procedures including review and approval of protocols

5. **Computer systems**

(Short description)

- 5.1 Hardware
- 5.2 Software (and version number) used (e.g. in the bioanalytical laboratory, in pharmacokinetic and statistical analysis) and change control procedure
- 5.3 Data management systems (include a procedural flow chart and a brief description of query generation and resolution)
- 5.4. Security procedures
- 5.5 Electronic exchange of confidential information
- 5.6 Brief description of validation programme
- 5.7 Back-up and storage of electronic data

6. **Equipment and instruments**

- 6.1 Brief description of major equipment and instruments (a list of equipment is not required)
- 6.2 Qualification, maintenance and calibration programme, including the temperature recording systems

7. **Documentation**

- 7.1 Briefly describe document management systems
- 7.2 Project work flow including quality assurance and control process
- 7.3 Preparation of protocols
- 7.4 Preparation of informed consent forms and subject information forms
- 7.5 Preparation of report forms
- 7.6 Preparation of final report

8. **Safety monitoring**

(Brief description)

Adverse drug reaction reporting procedure

Provisions made for emergencies, including protocols and equipment available

9. **Investigational medicinal products and comparator products**

(Brief description)

- 9.1 Acquisition, storage, handling, sampling and disposal
- 9.2 Pharmacy and dispensing

10. **Pathology**

- 10.1 Biological sample collection and storage
- 10.2 Handling and analysis of biological samples

11. **Bioanalytical laboratory**

(Brief description)

- 11.1 Method development and validation
- 11.2 Reference standard materials used for preparation of calibration standards and quality control samples
- 11.3 Biological matrix storage, and handling of matrix samples
- 11.4 Analysis of unknown samples

11.5 Preparation and labelling of reagents

11.6 Storage of samples

11.7 Stability procedures

11.8 Waste management

12. **Biostatistics**

12.1 Data processing and analysis

12.2 Data management

13. **Study volunteers**

13.1 Procedure for recruitment

13.2 Collecting information on volunteers (e.g. databank), while confidentiality is maintained

13.3 Procedure for obtaining informed consent

14. **Other information**

14.1 Power supply system — uninterrupted power supply and generator availability and capacity

14.2 Brief description of any other activities performed on site by the CRO

14.3 Any other information which the CRO may feel it appropriate to add

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The International Pharmacopoeia, fourth edition.

Volume 1: general notices; monographs for pharmaceutical substances (A–O)

Volume 2: monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents.

2006 (1500 pages), also available in CD-ROM format and online

First supplement: general notices; monographs for pharmaceutical substances; monographs for dosage forms; general and specific monographs; methods of analysis; International Chemical Reference Substances; International Infrared Reference Spectra; reagents, test solutions and volumetric solutions.

2008 (309 pages), also available in CD-ROM format and online

**Basic tests for drugs: pharmaceutical substances,
medicinal plant materials and dosage forms**

1998 (94 pages)

Basic tests for pharmaceutical dosage forms

1991 (134 pages)

**Quality Assurance of Pharmaceuticals: a compendium
of guidelines and related materials**

Volume 1: 1997 (244 pages)

Volume 2: good manufacturing practices and inspection.

Second updated edition, 2007 (409 pages)

Also available on: WHO training modules on GMP. A resource and study pack for trainers, 2007 (CD-ROM).

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Forty-third report.

WHO Technical Report Series, No. 953, 2009 (161 pages)

International nonproprietary names (INN) for pharmaceutical substances

Cumulative list no. 13

2010 (available in CD-ROM format only)

The selection and use of essential medicines

Report of the WHO Expert Committee (including the 16th WHO Model List of Essential Medicines and the 2nd WHO Model List for Children).

WHO Technical Report Series, No. 958, 2010 (174 pages)

WHO Expert Committee on Biological Standardization

Fifty-sixth report.

WHO Technical Report Series, No. 941, 2007 (340 pages)

Further information on these and other WHO publications can be obtained from
WHO Press, World Health Organization, 1211 Geneva 27, Switzerland
(tel. +41 22 791 3264; fax: +41 22 791 4857;
e-mail: bookorders@who.int; order online: <http://www.who.int/bookorders>)

The Expert Committee on Specifications for Pharmaceutical Preparations works towards clear, independent and practical standards and guidelines for the quality assurance of medicines. Standards are developed by the Committee through worldwide consultation and an international consensus-building process. The following new guidelines were adopted and recommended for use: good practices for pharmaceutical quality control laboratories; supplementary guidelines for active pharmaceutical ingredients; good manufacturing practices for pharmaceutical products containing hazardous substances; good manufacturing practices for sterile pharmaceutical products; good distribution practices for pharmaceutical products; guidelines on the requalification of prequalified dossiers: and guidelines for the preparation of a contract research organization master file.

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Annex 3

WHO good manufacturing practices for pharmaceutical products containing hazardous substances

1. Introduction
2. General
3. Glossary
4. Risk assessment
5. Product protection
6. Personal protection equipment and breathing air systems
7. Environmental protection
8. Facility layout
9. Air-handling systems
10. Air-handling units
11. Safe change filter housings
12. Personnel decontamination systems
13. Effluent treatment
14. Maintenance
15. Qualification and validation

References

1. Introduction

1.1 These guidelines set out good practices applicable to facilities handling pharmaceutical products (including active pharmaceutical ingredients (APIs)) that contain hazardous substances such as certain hormones, steroids or cytotoxins. They do not replace national legislation for protection of the environment and personnel. Other WHO guides to good manufacturing practices (GMP) and regulations need to be observed in addition to the workers' safety criteria (1–4).

1.2 These guidelines are to be read in conjunction with other WHO GMP guidelines with respect to building finishes and general services installations, among others. See the reference list for relevant publications which serve as additional background material. The primary focus of these guidelines is on the air-conditioning and ventilation systems of the facility; however, the document also provides some guidance on personnel protection.

1.3 The areas to which this document applies include all zones where the handling of products could lead to cross-contamination, exposure of personnel, or discharge to the environment. This includes research and development facilities, and the sites of API manufacturing and storage and of finished product manufacturing.

1.4 Where possible products should be manufactured in closed systems.

2. General

2.1 Facilities should be designed and operated in accordance with the main GMP principles, as follows:

- to ensure quality of product;
- to protect the operators from possible harmful effects of products containing hazardous substances; and
- to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.

2.2 The production of certain products containing hazardous substances should generally be conducted in separate, dedicated, self-contained facilities.

These *self-contained facilities* may be in the same building as another facility but should be separated by a physical barrier and have, e.g. separate entrances, staff facilities and air-handling systems. The extent of the separation from adjacent facilities and sharing of common services should be determined by risk assessment.

2.3 In general these manufacturing facilities should be regarded as containment facilities.

2.4 The effective operation of a facility may require the combination of some or all of the following aspects:

- appropriate facility design and layout, with the emphasis on safely containing the materials being handled. Manufacturing processes using closed systems or barrier technology enhance operator and product protection;
- manufacturing process controls including adherence to standard operating procedures (SOPs);
- appropriately designed environmental control systems (ECS) or heating, ventilation and air-conditioning (HVAC);
- extraction systems;
- personal protective equipment (PPE);
- appropriate degowning and decontamination procedures;
- industrial hygiene (monitoring staff exposure levels);
- medical surveillance (monitoring staff exposure levels); and
- administrative controls.

3. **Glossary**

The definitions given below apply to terms used in these guidelines. They may have a different meaning in other contexts.

action limit

The action limit is reached when the acceptance criteria of a critical parameter have been exceeded. Results outside these limits will require specified action and investigation.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

air-handling unit (AHU)

The air-handling unit serves to condition the air and provide the required air movement within a facility.

airlock

An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of

controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods (this can be a personnel airlock (PAL) or a material airlock (MAL)).

alert limit

The alert limit is reached when the normal operating range of a critical parameter has been exceeded, indicating that corrective measures may need to be taken to prevent the action limit being reached.

barrier technology

A system designed to segregate people from the product, contain contaminants or segregate two areas, which could be a barrier isolator (BI) or a restricted access barrier system (RABS):

- A BI is a unit supplied with high-efficiency particulate air (HEPA) filtered air that provides uncompromised continuous isolation of its interior from the external environment, including surrounding clean room air and personnel.
- A RABS is a type of barrier system that reduces or eliminates interventions into the critical zone. In practice, its level of contamination control is less than that of a barrier isolator.

clean room

A room or area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

commissioning

Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at the conclusion of project construction but prior to validation.

containment

A process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

contamination

The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.

cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or material during production.

design condition

Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

environmental control system (ECS)

Environmental control system, also referred to as heating, ventilation and air-conditioning (HVAC).

facility

The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

hazardous substance or product

A product or substance that may present a substantial risk of injury, to health or to the environment.

heating, ventilation and air-conditioning (HVAC)

Heating, ventilation and air-conditioning, also referred to as environmental control system (ECS).

high efficiency particulate air (HEPA) filter

High efficiency particulate air filter.

ISO 14644

International standard relating to the design, classification and testing of clean environments (5).

laminar airflow (LAF)

A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow).

normal operating range

The range that the manufacturer selects as the acceptable values for a parameter during normal operations. This range must be within the operating range.

occupational exposure level (OEL)

Airborne concentration of substances that will not result in adverse effects to most healthy workers, exposed for 8 hours/day, 40 hours/week.

operating range

The range of validated critical parameters within which acceptable products can be manufactured.

personal protective equipment (PPE)

The necessary garments and equipment required to protect the operator in the workplace.

pressure cascade

A process whereby air flows from one area, which is maintained at a higher pressure, to another area at a lower pressure.

qualification

The planning, carrying out and recording of tests on equipment and a system, which forms part of the validated process, to demonstrate that it will perform as intended.

standard operating procedure (SOP)

An authorized written procedure, giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (e.g. operation of equipment, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

unidirectional airflow (UDAF)

A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines.

validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

4. **Risk assessment**

4.1 Not all products containing hazardous substances are equally potent and risk assessments should be carried out to determine the potential hazards to operators and to the environment. The risk assessment should also determine which phases of the product production and control cycles, from manufacture of the API to distribution of the finished product, would fall under the requirements of these guidelines. Risk assessments applicable to the environment should include airborne contamination as well as liquid effluent contamination.

4.2 Assuming that the risk assessment determines that the products or materials being handled pose a risk to the operators and/or the public and/or the environment, the guidelines to be followed for the design and operation of the facility should be as detailed in this document.

4.3 The toxicological data available, such as permissible occupational exposure levels (OEL) for the product, should be taken into account when conducting the risk assessment.

4.4 The risk assessment should take into account the national or international occupational health and safety requirements for OELs in the work environment.

5. **Product protection**

5.1 The requirement for producing quality products, with respect to protection from contamination and cross-contamination, clean room class of air, temperature and humidity should be as for other pharmaceutical products. These requirements are covered in other WHO GMP guidelines.

6. **Personal protection equipment and breathing air systems**

6.1 The fundamental design principle for a facility and its production equipment is to provide product containment and operator protection. Should the facility and equipment design not provide adequate product containment, operator protection should be provided. If facility and equipment design are adequate, a spillage or non-routine incident could cause a hazardous situation, in which case PPE should be available. Unless otherwise specified in the material safety data sheet, operators should be protected from exposure with an appropriate method, such as by wearing:

- flash-spun, high-density polyethylene fibre material suits or impervious washable protective suits. Integral hoods may be required depending on the respirator type used;
- flash-spun, high-density polyethylene fibre material shoes, lower leg covers or cleanable boots;
- suitable single-use, disposable gloves. Double gloves should be worn where direct active contact with the product cannot be avoided. Gloves should be taped or sealed on to the protective suit sleeves; and
- respirator eye and face protection with associated breathing air systems.

6.2 Where breathing air systems are used, these should be provided to supply safe breathing air to the operators to prevent them from inhaling air from within the facility. Personnel should be appropriately trained and assessed in the use of these systems before they can enter the area. The breathing air systems should comprise a protective face mask, which should form an integral part of a protective suit. The breathing air systems could be any of the systems described below:

- a central air supply system which connects to the operator's face mask by means of flexible hoses and quick coupling sockets, also called an airline respirator (AR). The air connection should incorporate a one-way air system to prevent contaminated air entering the face mask during connection or disconnection. The air supply should be treated to ensure a temperature and level of humidity that are comfortable for the operator. The air source could be a high pressure fan or an air compressor. If an air compressor is used, it should be of the oil-free type or have suitable oil removal filters fitted;
- a self-contained breathing apparatus (SCBA) or powered air purifying respirator (PAPR) that is securely attached to the operator's belt and connects to the operator's face mask. This system draws air from the room in which the operator is working and the air supply is delivered to the face mask by means of a battery-driven fan. The AR provides superior protection to the PAPR apparatus;
- for zones with lower contamination levels, a half-mask high efficiency particulate air filter (HEPA) cartridge respirator of N95-type paper filter mask may be acceptable.

6.3 The selection of the respirator type is based on the relationship between the accepted OEL and the respirator-certified protection factor (PF).

6.4 The air supplies should be filtered through a final filter, which should be a HEPA filter rated as an H13 filter according to EN 1822 (European Norm). The supply of breathing air into the face mask and/or protective suit should result in the interior of the mask and suit being at a positive pressure relative to the facility environment.

6.5 Central breathing air supply systems should have a 100% back-up system in the event of the main system failing. This could be in the form of a gas bottle system with at least 5 minutes supply. Changeover from the normal supply to the back-up supply should be automatic. The system should have a monitoring system and send alarm signals to a permanently manned location in the following situations:

- failure of main air supply;
- temperature out of specification (OOS);
- humidity OOS;
- carbon dioxide (CO₂) OOS;
- carbon monoxide (CO) OOS; and
- sulfur dioxide (SO₂) OOS.

6.6 Breathing air should be filtered by means of pre-filters, coalescing filters and final filters to have the minimum air quality specifications of ISO 8573-1 3-9-1 and EN 12021:1999.

6.7 Where air is delivered through a central system the piping should not cause any contamination to be liberated into the air stream. Stainless steel piping is preferred. The final filters should be as close as possible to the operator connection points. The operator hose connection to the air supply should be a dedicated connection specific to the breathing air system (to avoid inadvertent connection to a different gas system).

7. Environmental protection

7.1 Due to the hazardous nature of the products being handled in the facility, neither the product nor its residues should be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.

7.2 The external atmosphere and the public in the vicinity of the facility should be protected from possible harm from hazardous substances.

7.3 If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.

7.4 Exhaust air filtration to ensure environmental protection is discussed in section 11.

8. Facility layout

8.1 The premises should be designed and constructed to prevent the ingress or egress of contaminants. In drawing up the facility design, attention should be paid to the level of containment provided by the equipment.

8.2 The link between the interior and exterior of the premises should be through airlocks (PAL and/or MAL), changing rooms, pass boxes, pass-through hatches, decontamination devices, etc. These entry and exit doors for materials and personnel should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.

8.3 The changing rooms should have an arrangement with a step-over-bench. The facilities on the exit side should incorporate showers for the operators.

8.4 The premises should be laid out and designed so as to facilitate the required pressure cascades and containment.

8.5 The premises (and equipment) should be appropriately designed and installed to facilitate cleaning and decontamination.

8.6 The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) to ensure that the designation and conditions of use of all the rooms are correctly shown.

8.7 The flow of people and products should be clearly marked on the layouts and plans.

8.8 The activities carried out in the vicinity of the site should be indicated.

8.9 Plans should describe the ventilation systems, indicating inlets and outlets, in relation to other facility air inlet and outlet points.

8.10 The facility should be a well-sealed structure with no air leakage through ceilings, cracks or service areas.

8.11 Areas of the facility where exposed product presents a risk should be maintained at a negative air pressure relative to the environment.

9. **Air-handling systems**

9.1 The HVAC system should be appropriately designed, installed and maintained to ensure protection of product, personnel and the environment.

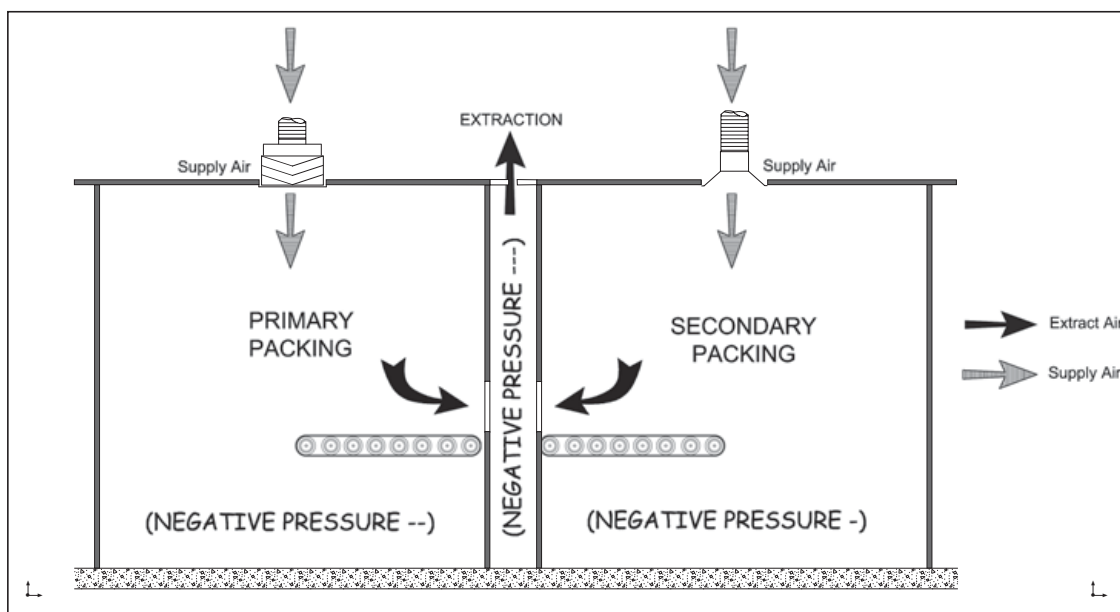
9.2 The principles of airflow direction, air filtration standards, temperature, humidity and related parameters should comply with the minimum requirements as set out in Annex 2 of the fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2006 (2).

9.3 Facilities and premises dealing with hazardous substances should have the following basic air-handling characteristics:

- There should be no direct venting of air to the outside.
- Air-conditioning or ventilation should result in a negative pressure relative to the outside. Air pressure differentials should be such that there is no uncontrolled flow of air between the work area and the external environment.
- Appropriate air pressure alarm systems should be provided to warn of any pressure cascade reversal or loss of design pressure status. The appropriate design, alert and action limits should be in place. System redundancies should be in place to respond appropriately to pressure cascade failure.
- The starting and stopping of the supply and exhaust air fan should be synchronized such that the premises remain at a negative pressure during start-up and shut-down.
- The air pressure cascade within the facility, although negative relative to the environment, should comply with normal pharmaceutical pressure cascade requirements with regards to product protection, dust containment and personnel protection.
- Visual indication of the status of room pressures should be provided in each room.
- Air should be exhausted to the outside through HEPA filters and not be recirculated except to the same area, and provided that a further HEPA filtration stage is applied to the return air. Where HEPA filters are

Figure 1

Typical airflow pattern for contaminant



mentioned in these guidelines, this refers to HEPA filters with a minimum rating of H13 according to EN 1822.

- Where possible, single-pass air-handling systems with no recirculation should be provided.
- Exhaust air or return air should be filtered through a safe-change or bag-in-bag-out filter housing. The filter housing should contain pre-filters and HEPA filters, both of which should be removable with the safe bagging system.
- Changing rooms should be supplied with air filtered to the same standard as that for the work area they serve.
- Airlocks, pass-through hatches, etc., should have supply and extract air to provide the necessary air pressure cascade and containment. The final, or containment perimeter, airlock or pass-through hatch bordering on an external or non-GMP area should be at a positive pressure relative to the environment, to prevent the ingress of contaminants to the facility.
- If the facility provides insufficient containment, and operators' garments are contaminated with dust, the operators leaving the containment area should pass through a decontamination system, e.g. air showers or a mist shower system, to assist with removing or controlling dust particles on their garments. Operators should follow this route before de-gowning to use the ablutions or canteen facilities. All garments leaving the facility for laundering should be safely bagged. Appropriate means for protecting laundry staff and prevention of contamination of other garments from non-hazardous facilities should be in place.

9.4 If required, appropriate measures should be taken to prevent airflow from the primary packing area (through the conveyor “mouse hole”) to the secondary packing area.

Note: This could be overcome by having a pass-through chamber over the “mouse hole”, which is maintained at a negative pressure to both primary and secondary packing. This typical arrangement is illustrated in Figure 1. This principle can be applied to other situations where containment from two sides is required.

9.5 Where possible, HEPA filters in the supply air system should be terminally mounted to provide protection against back-flow cross-contamination in the event of a failure in the supply airflow.

9.6 In some cases consideration can be given to the use of biosafety cabinets, isolation systems or glove boxes as a means for containment and operator protection.

9.7 There should be a system description including schematic drawings detailing the filters and their specifications, the number of air changes per hour, pressure gradients, clean room classes and related specifications. These should be available for inspection.

9.8 There should be an indication of pressure gradients that are monitored by means of digital or analogue pressure indicators.

9.9 Consideration should be given to providing an emergency power supply, e.g. diesel generators, to ensure that safe operation of the premises and systems can be maintained at all times.

10. **Air-handling units**

10.1 The air-handling units (AHUs) supplying air to the facility should conform to AHU requirements as detailed in *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials (1)* and *Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms (2)* and the filtration should be consistent with the zone concepts and product protection required.

10.2 The decision to use return air or recirculated air should be made on the basis of a risk assessment.

10.3 Where a full fresh-air or single-pass system is used, an energy recovery wheel could be considered. In such cases, there should not be any potential for air leakage between the supply air and exhaust air as it passes through the wheel. The relative pressures between supply and exhaust air systems should be such that the exhaust-air system operates at a lower

pressure than the supply system. (Alternatives to the energy recovery wheel, such as crossover plate heat exchangers, heat pipes and water coil heat exchangers, may be used.)

10.4 Risk management principles should be applied to address the potential of cross-contamination where energy wheels are used.

10.5 If return air is to be recirculated it should pass through a safe change filtration system before being introduced back into the supply AHU. The return air fan could form part of the AHU; however, the safe change filter should be a dedicated unit. With this arrangement the return air passes through two sets of HEPA filters in series, i.e. the return air filters in the safe change housing and the supply air HEPA filters. The supply air HEPA filters could either be located in the AHU or terminally located at the supply diffusers, depending on the clean room classification of the facility.

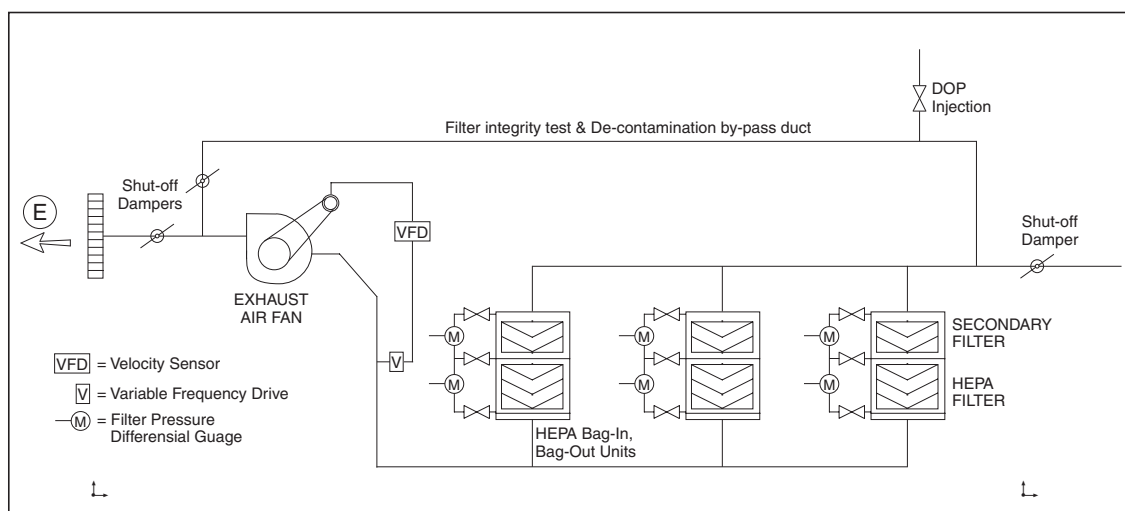
10.6 The starting and stopping of the supply and exhaust air fans, and associated system ventilation fans, should be synchronized such that the premises retain their design pressure and flow relationships during start-up and shut-down. Processing should stop when the fans are not running. This fan interlock sequence should also apply if any fan should fail, to ensure that there is no airflow reversal in the system.

11. Safe change filter housings

11.1 Safe change or bag-in-bag-out filter housings should be suitably designed to provide operator protection and to prevent dust from the filters entering the atmosphere when filters are changed.

Figure 2

Safe change filter bypass arrangement



11.2 The final filters on the safe change unit should be HEPA filters with at least an H13 classification according to EN 1822 filter standards. For dusty return, air pre-filtration may also be required to prolong the life of the HEPA filters. The pre-filtration filters should also be removable through the bag-in-bag-out method.

11.3 For exhaust systems where the discharge contaminant is considered particularly hazardous, two banks of HEPA filters in series should be considered to provide additional protection should the first filter fail.

11.4 All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading and remaining lifespan of the filters. Connection to these gauges should be copper or stainless steel and not plastic tubing, which could perish causing a contamination hazard. The tube connections on the filter casing should be provided with stopcocks, for safe removal or calibration of gauges.

11.5 Monitoring of filters should be done at regular intervals to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination.

11.6 Computer-based data monitoring systems may be installed to monitor filter condition.

11.7 Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.

11.8 Installed filter leakage tests should be performed in accordance with ISO 14644-3. Injection ports (upstream) and access ports (downstream) should, therefore, be provided for this purpose.

11.9 The exhaust air fan on a safe change filter system should be located after the filters so that the filter housing is maintained at a negative pressure. This poses a difficulty when carrying out filter integrity tests, and for this reason a bypass damper system should be provided, as illustrated in Figure 2, so that air can be circulated through the HEPA filters, while the scanning ports are open. Alternatively an independent booster fan system can be used, with appropriate shut-off dampers.

11.10 The bypass arrangement as shown in Figure 2 also permits decontamination of the filters by means of circulation of a sanitizing agent.

11.11 All exhaust systems from the facility, including dust extraction systems, vacuum system exhaust, fluid bed drier exhaust and coating pan exhaust, should be passed through safe change filter housings before being exhausted to the atmosphere.

11.12 All exhaust points outside the building should be located as far as possible from air entry points, and exit points should be at a high level to minimize the possibility of re-entrainment of exhaust air. Dominant and seasonal wind directions should be taken into account when positioning exhaust and supply points.

11.13 Where excessively dust-laden air is handled, a dust collector or bag house should be considered, with the dust collector being located in an enclosed room maintained at a negative pressure. Access control, maintenance staff, personal protection equipment (PPE) and breathing air systems should then be provided to protect the operators during removal of dust from the collector bins.

11.14 Portable vacuum cleaners and portable dust collectors should be fitted with H13 HEPA filters. These types of units should be emptied and cleaned in a room which is under negative pressure relative to the environment. Personnel should be provided with suitable PPE.

11.15 Records of the safe disposal of all contaminated filters and dust should be kept.

12. **Personnel decontamination systems**

12.1 If required, a means of preventing contaminants from leaving the facility on the garments of personnel should be provided. This could be in the form of an air shower; mist shower, water shower or appropriate device.

12.2 An air shower comprises an airlock where high velocity air is supplied through air nozzles (e.g. from the sides of the airlock) in order to dislodge dust particles. Air extraction grilles (e.g. at low level) should draw the air away and return it to the filtration system. Some air showers may also incorporate a vertical unidirectional airflow section at the exit end, to flush contaminants away.

Note: When air showers are used these should be correctly designed to effectively extract dust.

Air filtration of the supply air and return or exhaust air should comply with the same filtration standards as used in the manufacturing facility. Normally the fan should be activated by opening the door as the operator enters the shower, with a timing device on the exit door interlock to allow sufficient time for the decontamination process to be effective.

12.3 Flushing devices similar to air or mist showers for personnel could be used at material exits to assist with removing contaminants.

12.4 Wet mist or fog decontamination systems for operators can be employed for deactivating contaminants on the operator's garments, or

causing contaminants to adhere to the garments so that they are not easily liberated.

12.5 Personnel should change into clean garments after having taken a shower.

13. **Effluent treatment**

13.1 Liquid and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.

13.2 All effluent should be disposed of in a safe manner, and the means of disposal should be documented. Where external contractors are used for effluent disposal they should have certification authorizing them to handle and treat hazardous products.

14. **Maintenance**

14.1 The efficient and safe operation of a facility handling hazardous materials is reliant on regular maintenance being carried out, to ensure that all parameters remain within specified tolerances. See *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials (1)* or WHO Technical Report Series, No. 937, Annex 2, section 8.3 (2) for further details on maintenance.

15. **Qualification and validation**

15.1 System qualification and validation should be carried out as described in other WHO guidelines.

References

1. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2*, 2nd updated ed. *Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007.
2. Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 2 (WHO Technical Report Series, No. 937).
3. *Health Canada: Laboratory biosafety guidelines*, 3rd ed. Ottawa, Health Canada, 2004.
4. WHO good manufacturing practices for sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization, 2010, Annex 4 (WHO Technical Report Series, No. 957).
5. ISO: International Standard. *Clean rooms and associated controlled environments. ISO 14644*. Geneva, International Organization for Standardization.

Annex 4

WHO good manufacturing practices for sterile pharmaceutical products

Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations in its thirty-sixth report in 1999 adopted *WHO good manufacturing practices for sterile pharmaceutical products* (WHO Technical Report Series, No. 902, 2002, Annex 6) (http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf); and published in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2. 2nd updated ed. Good manufacturing practices and inspection* (2007) (1).

Following implementation of these WHO good manufacturing practices (GMP) within the context of the WHO Prequalification Programme, a proposal for revision is being submitted to take into consideration new developments. The proposal for revision of the above-mentioned guidance is being made to bring the WHO GMP into line with International Standardization Organization standard ISO 14644-1 (2) and recent practices of the United States (3), Japan (4), the European Union (5) and the Pharmaceutical Inspection Co-operation Scheme.

- New chapters on Isolator technology and Blow/fill/seal technology have been added to the document.
- The chapter on Finishing of sterile products has been amended and provisions have been given for capping of vials.
- The chapter entitled Manufacture of sterile preparations has been amended and provisions have been given for clean room and clean-air device monitoring.

Implementation of these new practices may need to be undertaken for certain parts using a step-wise approach, especially the part relating to the provision for capping in a clean or sterile environment, as this is currently not implemented in most industries.

On the basis of the above, the following text is proposed to replace the previously published guidance.

WHO good manufacturing practices for sterile pharmaceutical products

1. General considerations
2. Quality control
3. Sanitation
4. Manufacture of sterile preparations
5. Sterilization
6. Terminal sterilization
7. Aseptic processing and sterilization by filtration
8. Isolator technology
9. Blow/fill/seal technology
10. Personnel
11. Premises
12. Equipment
13. Finishing of sterile products

References

1. **General considerations**

1.1 The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.

1.2 The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within the clean area. These areas are classified into four grades (see section 4).

Manufacturing operations are divided here into two categories:

- first, those where the product is terminally sterilized; and
- second, those which are conducted aseptically at some or all stages.

2. **Quality control**

2.1 The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.

2.2 Samples taken for sterility testing should be representative of the whole of the batch but should, in particular, include samples taken from parts of the batch considered to be most at risk of contamination, for example:

- for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;
- for products that have been heat sterilized in their final containers, consideration should be given to taking samples from that part of the load that is potentially the coolest.

2.3 The sterility of the finished product is assured by validation of the sterilization cycle in the case of terminally sterilized products, and by “media simulation” or “media fill” runs for aseptically processed products. Batch-processing records and, in the case of aseptic processing, environmental quality records, should be examined in conjunction with the results of the sterility tests. The sterility test procedure should be validated for a given product. Pharmacopoeial methods should be used for the validation and performance of the sterility test. In those cases where parametric release has been authorized in place of sterility testing special attention should be paid to the validation and the monitoring of the entire manufacturing process.

2.4 For injectable products the water for injection and the intermediate, if appropriate, and finished products should be monitored for endotoxins,

using an established pharmacopoeial method that has been validated for each type of product. For large-volume infusion solutions, such monitoring of water or intermediates should always be done, in addition to any tests required by an approved monograph for the finished product. When a sample fails a test, the cause of the failure should be investigated and necessary action should be taken. Alternative methods to those in the pharmacopoeias may be used if they are validated, justified and authorized.

2.5 The use of rapid microbiological methods to replace the traditional microbiological methods, and to obtain earlier results on the microbiological quality of, for example, water, the environment or bioburden, could be considered if appropriately validated and if a comparative assessment of the proposed rapid method is performed against the pharmacopoeial method.

3. **Sanitation**

3.1 The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with an approved written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be regularly undertaken to detect contamination or the presence of an organism against which the cleaning procedure is ineffective. Interactions between different cleaning materials should be validated. Appropriate cleaning validation should be carried out to ensure disinfectant residuals can be detected and are removed by the cleaning process.

3.2 Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilized. Disinfectants and detergents used in grade A and B areas should be sterile before use.

3.3 A disinfectant programme should also include a sporicidal agent since many common disinfectants are ineffective against spores. The effectiveness of cleaning and disinfectant procedures should be demonstrated.

3.4. Fumigation of clean areas may be useful for reducing microbial contamination in inaccessible places.

4. **Manufacture of sterile preparations**

4.1 Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate level of environmental cleanliness in the operational state to minimize the risks of particulate or microbial contamination of the product or materials being handled.

4.2 Detailed information on methods for determining the microbiological and particulate cleanliness of air, surfaces, etc., is not given in these guidelines.

ISO 14644-1 (2) should be used for classification of cleanliness according to concentration of airborne particles (determination of number of sample locations, calculation of sample size and evaluation of classification from the data obtained). Table 1 should also be used to define the levels to be used as the basis for monitoring clean areas for airborne particles.

4.3 For the manufacture of sterile pharmaceutical preparations, four grades of clean areas are distinguished as follows:

- *grade A*: The local zone for high-risk operations, e.g. filling and making aseptic connections. Normally such conditions are achieved by using a unidirectional airflow workstation. Unidirectional airflow systems should provide a homogeneous air speed of 0.36–0.54 m/s (guidance value) at a defined test position 15–30 cm below the terminal filter or air distributor system. The velocity at working level should not be less than 0.36 m/s. The uniformity and effectiveness of the unidirectional airflow should be demonstrated by undertaking airflow visualization tests;
- *grade B*: In aseptic preparation and filling, this is the background environment for the grade A zone;
- *grades C and D*: Clean areas for carrying out less critical stages in the manufacture of sterile products or carrying out activities during which the product is not directly exposed (i.e. aseptic connection with aseptic connectors and operations in a closed system).

A unidirectional airflow and lower velocities may be used in closed isolators and glove boxes.

4.4 In order to reach the B, C and D air grades the number of air changes should be appropriate for the size of the room and the equipment and personnel present in it.

4.5 High-efficiency particulate air (HEPA) filters should be subjected to an installed filter leakage test in accordance with ISO 14644-3 (6) at a recommended interval of every 6 months, but not exceeding 12 months. The purpose of performing regular leak tests is to ensure the filter media, filter frame and filter seal are free from leaks. The aerosol selected for HEPA leak testing should not support microbial growth and should be composed of a sufficient number or mass of particles. HEPA filter patching is allowed at the filter manufacturer and in situ operation provided that the patch sizes and procedures follow the recommendations of ISO 1822-4 (7).

4.6 Clean room and clean-air device classification

4.6.1 Clean rooms and clean-air devices should be classified in accordance with ISO 14644 (2, 6–9).

4.6.1.1 Classification should be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each grade is given in Table 1.

Table 1

Maximum permitted airborne particle concentration

	Maximum permitted number of particles per m ³ greater than or equal to the tabulated size			
	At rest ^a		In operation ^b	
Grade	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

^a The “at rest” state is the condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

^b The “in operation” state is the condition where the installation is functioning in the defined operating mode and the specified number of personnel is present. The areas and their associated environmental control systems should be designed to achieve both the “at rest” and “in operation” states.

4.6.2 For classification purposes, ISO 14644-1 (2) methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method for evaluation of the data collected. For classification of grade A zones (at rest and operational) and grade B zones (at rest), the minimum sample volume is based on the ISO 5 limit for the number of particles $\geq 0.5 \mu\text{m}$ (3520). Similarly, for classification of grade B (operational), grade C (at rest and operational), and grade D (at rest), the minimum sample volume is based on the class limits for particles $\geq 0.5 \mu\text{m}$ shown in Table 1.

For classification purposes in grade A zones, a minimum sample volume of 1 m³ should be taken per sample location. Referring to Table 1, for grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles $\geq 5.0 \mu\text{m}$. For grade B (at rest) the airborne particle classification is ISO 5 for both particle sizes considered. For grade C (at rest and in operation) the airborne particle classification is ISO 7 and ISO 8, respectively. For grade D (at rest) the airborne particle classification is ISO 8. For classification purposes ISO 14644-1 (2) methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest particle size considered and the method of evaluation of the data collected. The sample volume should be determined according to ISO 14644-1 (2) clause B.4.2. However, for lower grades

(grade C in operation and grade D at rest) the sample volume per location should be at least 2 litres and the sample time per location should be not less than 1 minute. There should not be less than 3 sample locations per room.

4.6.3 Portable particle counters with a short length of sample tubing should be used for classification purposes to avoid the loss of particles $\geq 5.0 \mu\text{m}$. Isokinetic sample heads should be used in unidirectional airflow systems.

4.6.4 “In operation” classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. ISO 14644-2 (8) provides information on testing to demonstrate continued compliance with the assigned cleanliness classification.

4.7 Clean room and clean-air device monitoring

4.7.1 Clean rooms and clean-air devices should be routinely monitored while in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean-air devices.

4.7.2 For grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, for example, live organisms and radiological hazards. In such cases monitoring during routine equipment set-up operations should be undertaken before exposure to the risk. Monitoring during simulated operations should also be performed. The grade A zone should be monitored at a frequency and sample size such that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of $\geq 5.0 \mu\text{m}$ particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

4.7.3 It is recommended that a similar system be used for grade B zones, although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent grade A and B zones. The grade B zone should be monitored at a frequency and with a sample size such that changes in levels of contamination and any deterioration of the system would be captured and alarms triggered if alert limits are exceeded.

4.7.4 Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points

connected by manifold to a single particle counter; or multiple small particle counters located near monitoring points and networked to a data acquisition system. Combinations of systems can also be used. The system selected should be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing should be considered in the context of particle losses in the tubing. The selection of the monitoring system should take account of any risk presented by the materials used in the manufacturing operation, for example, those involving live organisms or radiopharmaceuticals.

4.7.5 The sizes of samples taken for monitoring purposes using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean-air devices.

4.7.6 The airborne particle conditions given in Table 1 for the “at rest” state should be achieved in the absence of the operating personnel after a short “clean-up” or “recovery” period of about 15–20 minutes (guidance value), after completion of the operations. The particulate conditions given in Table 1 for grade A “in operation” should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. The “clean-up” or “recovery” test should demonstrate a change in particle concentration by a factor of 100 within the prescribed time (ISO 14644-3 clause B.12) (6).

4.7.7 In order to demonstrate control of the cleanliness of the various clean areas during operation, they should be monitored for airborne particles and microbial contamination. In addition to “at rest” and “in operation” classification, airborne particles should be monitored periodically “in operation” at critical locations. The sampling plan need not be the same as that used for classification. Locations and sample sizes should be determined based on an assessment of the process and contamination risk.

4.7.8 The monitoring of grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended “clean-up period” should be attained.

4.7.9 Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.

4.7.10 Examples of operations to be carried out in the various grades are given in Table 2 (see also sections 4.14–4.22).

Table 2

Examples of operations to be carried out in the various grades

Grade	Examples of operations for terminally sterilized products (see sections 4.14–4.17)
A	Filling of products when unusually at risk
C	Preparation of solutions when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for aseptic preparations (see sections 4.18–4.22)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

4.8 To control the microbiological cleanliness of the cleanliness grades A–D in operation the clean areas should be monitored. Where aseptic operations are performed, monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitization.

4.9 Levels of detection of microbial contamination should be established for the purpose of setting alert and action levels and for monitoring the trends in environmental cleanliness in the facility. Limits expressed in colony-forming units (CFU) for the microbiological monitoring of clean areas in operation are given in Table 3. The sampling methods and numerical values included in the table are not intended to represent specifications, but are for information only.

Table 3

Recommended limits for microbial contamination^a

Grade	Air sample (CFU/m ³)	Settle plates (diameter 90 mm) (CFU/4 hours) ^b	Contact plates (diameter 55 mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

CFU, colony-forming units.

^a These are average values.

^b Individual settle plates may be exposed for less than 4 hours.

4.10 Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If the action limits are exceeded or a trend is identified in the alert levels, investigation should be initiated and the appropriate corrective actions should be taken, as prescribed in the operating procedures.

4.11 The area grades as specified in sections 4.12 to 4.20 should be selected by the manufacturer on the basis of the nature of the process operations being performed and validation runs (e.g. aseptic media fills or others types of process simulations) are used to establish processing hold times and a maximum fill duration. The determination of an appropriate process area environment and a time limit should be based on the microbial contamination (bioburden) found.

terminally sterilized products

4.12 Components and most products should be prepared in at least a grade D environment to ensure low microbial bioburden and particulate counts prior to filtration and sterilization. Where the product is at unusual risk of microbial contamination (e.g. because it actively supports microbial growth, must be held for a long period before sterilization, or is necessarily processed mainly in open vessels), the preparation should generally be done in a grade C environment.

4.13 The filling of products for terminal sterilization should generally be done in at least a grade C environment.

4.14 Where the product is at unusual risk of contamination from the environment (e.g. because the filling operation is slow, the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing), the filling should be done in a grade A zone with at least a grade C background.

4.15 The preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilization.

Aseptic preparation

4.16 Components after washing should be handled in at least a grade D environment. The handling of sterile starting materials and components, unless subjected to sterilization or filtration through a microorganism-retaining filter later in the process, should be undertaken in a grade A environment with a grade B background.

4.17 The preparation of solutions which are to be sterile-filtered during the process should be undertaken in a grade C environment (unless a closed system is used, in which case a Class D environment may be justifiable).

If not sterile-filtered (therefore an aseptic manipulation) the preparation of materials and products should be undertaken in a grade A environment with a grade B background.

4.18 The handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, should be undertaken in a grade A environment with a grade B background.

4.19 The transfer of partially closed containers, as used in freeze-drying, before stoppering is completed, should be undertaken either in a grade A environment with a grade B background or in sealed transfer trays in a grade B environment.

4.20 The preparation and filling of sterile ointments, creams, suspensions and emulsions should be undertaken in a grade A environment with a grade B background when the product is exposed and is not subsequently filtered.

Processing

4.21 Precautions to minimize contamination should be taken during all processing stages, including the stages before sterilization.

4.22 In general, preparations containing live microorganisms should not be made, nor should containers be filled in areas used for the processing of other pharmaceutical products. However, if the manufacturer can demonstrate and validate effective containment and decontamination of the live microorganisms, the use of multiproduct facilities may be justifiable. Vaccines consisting of dead organisms or of bacterial extracts may be dispensed into containers in the same premises as other sterile pharmaceutical products, provided that the inactivation procedure has been properly validated.

When multiproduct facilities are used to manufacture sterile preparations containing live microorganisms and other sterile pharmaceutical products, the manufacturer should demonstrate and validate the effective decontamination of the live microorganisms, in addition to precautions taken to minimize contamination.

4.23 Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium.

4.24 The process simulation test should imitate as closely as possible the routine aseptic manufacturing steps except where the activity may lead to any potential microbial contamination.

4.25 Process simulation tests should be performed as part of validation by running three consecutive satisfactory simulation tests. These tests should be repeated at defined intervals and after any significant modification to

the heating, ventilation and air-conditioning (HVAC)-system, equipment or process. Process simulation tests should incorporate activities and interventions known to occur during normal production as well as the worst-case situation. The process simulation tests should be representative of each shift and shift changeover to address any time-related and operational features.

4.26 The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following should apply:

- when filling fewer than 5000 units, no contaminated units should be detected;
- when filling 5000–10 000 units:
 - one contaminated unit should result in an investigation, including — consideration of a repeat media fill,
 - two contaminated units are considered cause for revalidation following investigation;
- when filling more than 10 000 units:
 - one contaminated unit should result in an investigation,
 - two contaminated units are considered cause for revalidation following investigation.

4.27 For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated. Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

4.28 Care should be taken to ensure that any validation does not compromise the processes.

4.29 Water sources, water-treatment equipment and treated water should be monitored regularly for chemicals, biological contamination and contamination with endotoxins to ensure that the water complies with the specifications appropriate to its use. Records should be maintained of the results of the monitoring and of any action taken (10).

4.30 Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum and the movement of personnel should be controlled and methodical, so as to avoid excessive shedding of particles and organisms due to over-vigorous activity. As far as possible, personnel should be excluded from grade A zones. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn and to reduce the risk of contamination liberated from the personnel.

4.31 The presence of containers and materials liable to generate fibres should be minimized in clean areas and avoided completely when aseptic work is in progress.

4.32 Components, bulk-product containers and equipment should be handled after the final cleaning process in such a way as to ensure that they are not recontaminated. The stage of processing of components as well as the bulk-product containers and equipment should be properly identified.

4.33 The interval between the washing and drying and the sterilization of components, bulk-product containers and equipment, as well as between sterilization and use, should be as short as possible and subject to a time-limit appropriate to the validated storage conditions.

4.34 The time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retaining filter should be as short as possible. A maximum permissible time should be set for each product that takes into account its composition and the prescribed method of storage.

4.35 Any gas that is used to purge a solution or blanket a product should be passed through a sterilizing filter.

4.36 The bioburden should be monitored before sterilization. There should be working limits on contamination immediately before sterilization, which are related to the efficiency of the method to be used. Bioburden assay should be performed on each batch for both aseptically filled products and terminally sterilized products. Where overkill sterilization parameters are set for terminally sterilized products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assay should be performed on each batch and considered as an in-process test. Where appropriate, the level of endotoxins should be monitored. All solutions, in particular large-volume infusion fluids, should be passed through a microorganism-retaining filter, if possible sited immediately before filling.

4.37 Components, bulk-product containers, equipment, and any other articles required in a clean area where aseptic work is in progress, should be sterilized and wherever possible passed into the area through double-ended sterilizers sealed into the wall. Other procedures that prevent the introduction of contamination may be acceptable in some circumstances.

4.38 The efficacy of any new processing procedure should be validated and the validation should be repeated at regular intervals thereafter or when any significant change is made in the process or equipment.

5. Sterilization

5.1 Whenever possible products intended to be sterile should be terminally sterilized by heat in their final container. Where it is not possible to carry out terminal sterilization by heating due to the instability of a formulation or incompatibility of a pack type (necessary to the administration of the product, e.g. plastic eye-dropper bottles), a decision should be taken to use an alternative method of terminal sterilization following filtration and/or aseptic processing.

5.2 Sterilization can be achieved by the use of moist or dry heat, by irradiation with ionizing radiation (noting that ultraviolet irradiation is not normally an acceptable method of sterilization), by ethylene oxide (or other suitable gaseous sterilizing agents), or by filtration with subsequent aseptic filling of sterile final containers. Each method has its advantages and disadvantages. Where possible and practicable, heat sterilization is the method of choice. In any case the sterilization process must be in accordance with the marketing and manufacturing authorizations.

5.3 The microbial contamination of starting materials should be minimal and their bioburden should be monitored before sterilization. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.

5.4 All sterilization processes should be validated. Particular attention should be paid when the adopted sterilization method is not in accordance with pharmacopoeial standards or other national standards, or when it is used for a preparation that is not a simple aqueous or oily solution, for example, colloidal suspensions.

5.5 Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators, where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

5.6 For effective sterilization the whole of the material should be subjected to the required treatment and the process should be designed to ensure that this is achieved.

5.7 Biological indicators should be considered only as an additional method of monitoring the sterilization process. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If they are used, strict precautions should be taken to avoid any transfer of microbial contamination from them.

5.8 There should be a clear means of differentiating products that have not been sterilized from those which have. Each basket, tray, or other carrier of products or components should be clearly labelled with the name of the material, its batch number and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used where appropriate to indicate whether or not a batch (or sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the batch is in fact sterile.

5.9 Validated loading patterns should be established for all sterilization processes.

5.10 Sterilization records should be available for each sterilization run. They should be approved as part of the batch-release procedure.

6. **Terminal sterilization**

Sterilization by heat

6.1 Each heat-sterilization cycle should be recorded by means of appropriate equipment of suitable accuracy and precision, e.g. on a time/temperature chart with a suitably large scale. The temperature should be recorded by a probe situated at the coolest part of the load or loaded chamber, this point having been determined during the validation; the temperature should preferably be checked against a second independent temperature probe located at the same position. Sterilization records should be available for each sterilization run and should be approved as part of the batch release procedure. Chemical or biological indicators may also be used but should not take the place of physical controls.

6.2 Sufficient time should be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time is started. This time should be determined for each type of load to be processed.

6.3 After the high-temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized.

Sterilization by moist heat

6.4 Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator.

The reading of the independent temperature indicator should be routinely checked against the reading on the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilization period. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.

6.5 The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows the removal of air and the penetration of steam but prevents recontamination after sterilization. Specially designed autoclavable stainless steel containers, that allow steam to enter and air to leave, can also be used. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.

6.6 Care should be taken to ensure that the steam used for sterilization is of suitable quality (chemical, microbiological and endotoxin analysis of condensate and physical examination of steam (such as dryness, superheat, and non-condensable gases)) and does not contain additives at a level that could cause contamination of the product or equipment. Steam used for sterilization should be tested regularly.

Sterilization by dry heat

6.7 Sterilization by dry heat may be suitable for non-aqueous liquids or dry-powder products.

The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. If air is supplied it should be passed through a microorganism-retaining filter (e.g. a HEPA filter). Where sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins are required as part of the validation.

Sterilization by radiation

6.8 Sterilization by radiation is used mainly for heat-sensitive materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilization.

6.9 If sterilization by radiation is done by an outside contractor, the manufacturer is responsible for ensuring that the requirements of section 6.8 are met and that the sterilization process is validated.

6.10 During the sterilization procedure the radiation dose should be measured. The dosimeters used for this purpose should be independent of

the dose rate and should provide a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbance should be read shortly after exposure to radiation. Radiation-sensitive colour discs may be used to differentiate between packages that have been subjected to irradiation and those that have not; they are not indicators of successful sterilization. The information obtained should constitute part of the batch record.

6.11 Validation procedures should ensure that consideration is given to the effects of variations in the density of the packages.

6.12 Material-handling procedures should prevent any mix-up of irradiated and non-irradiated materials. Each package should carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment.

6.13 The total radiation dose should be administered within a predetermined period.

Sterilization by gases and fumigants

6.14 Sterilization by gases and fumigants should only be used for finished products where there is no suitable alternative.

6.15 Various gases and fumigants may be used for sterilization (e.g. ethylene oxide and hydrogen peroxide vapour). Ethylene oxide should be used only when no other method is practicable. During process validation it should be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material concerned. These limits should be incorporated in the specifications.

6.16 Direct contact between gas and microorganisms is essential; precautions should therefore be taken to avoid the presence of organisms likely to be enclosed in materials such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

6.17 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. This requirement should be balanced against the need to minimize the waiting time before sterilization.

6.18 Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed

throughout the load. The information thus obtained should form part of the batch record.

6.19 Biological indicators should be stored and used according to the manufacturer's instructions and their performance checked by positive controls.

6.20 For each sterilization cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration. The pressure and temperature should be recorded on a chart throughout the cycle. The records should form part of the batch record.

6.21 After sterilization, the load should be stored in a controlled manner in ventilated conditions to allow concentrations of residual gas and reaction products to fall to their prescribed levels. This process should be validated.

7. Aseptic processing and sterilization by filtration

7.1 The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which has been sterilized by one of the above methods (see sections 5 and 6).

7.2 The operating conditions should be such as to prevent microbial contamination.

7.3 In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to:

- the environment;
- personnel;
- critical surfaces;
- container/closure sterilization and transfer procedures;
- the maximum holding period of the product before filling into the final container; and
- the sterilizing filter.

7.4 Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22 micron (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment. Filtration alone is not considered sufficient when sterilization in the final container is possible. Of the methods currently available, steam sterilization is to be preferred.

7.5 Owing to the potential additional risks of the filtration method as compared with other sterilization processes, a double-filter layer or second filtration through a further sterilized microorganism-retaining filter immediately prior to filling may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

7.6 The fibre-shedding characteristics of filters should be minimal (virtually zero). Asbestos-containing filters should not be used under any circumstances.

7.7 The integrity of the sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from these during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals. Consideration should be given to increased monitoring of filter integrity in processes that involve harsh conditions, e.g. the circulation of high-temperature air.

7.8 The same filter should not be used for more than one working day unless such use has been validated.

7.9 The filter should not affect the product either by removing ingredients from it or by releasing substances into it.

8. Isolator technology

8.1 The use of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbial contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for each zone can be realized. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from single-door to double-door designs to fully-sealed systems incorporating sterilization mechanisms.

8.2 The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high-risk manipulations, although it is recognized that unidirectional airflow may not exist in the working zone of all isolators and transfer devices.

8.3 The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled, and for aseptic processing it should be at least grade D.

8.4 Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example, the quality of the air inside and outside (background) the isolator, sanitization of the isolator, the transfer process and isolator integrity.

8.5 Monitoring should be done routinely and should include frequent leak testing of the isolator and the glove/sleeve system.

9. **Blow/fill/seal technology**

9.1 Blow/fill/seal units are purpose-built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A or B clothing is used. The environment should comply with the viable and non-viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products which are terminally sterilized should be installed in at least a grade D environment.

9.2 Because of this special technology, particular attention should be paid to at least the following:

- equipment design and qualification;
- validation and reproducibility of cleaning-in-place and sterilization-in-place;
- background clean room environment in which the equipment is located;
- operator training and clothing; and
- interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

10. **Personnel**

10.1 Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. As far as possible, inspections and controls should be conducted from outside such areas.

10.2 All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive initial and regular training in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology. When outside

staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.

10.3 Staff who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.

10.4 High standards of personal hygiene and cleanliness are essential and personnel involved in the manufacture of sterile preparations should be instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. The action to be taken in respect of personnel who might be introducing undue microbial hazards should be decided by a designated competent person.

10.5 Changing and washing should follow a written procedure designed to minimize the contamination of clean-area clothing or the carry-through of contaminants to clean areas. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.

10.6 Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilized or adequately sanitized) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least every working session. Operators working in grade A and B areas should wear sanitized goggles.

10.7 Wrist-watches, cosmetics and jewellery should not be worn in clean areas.

10.8 The clothing required for each grade is as follows:

- *Grade D.* The hair and, where relevant, beard and moustache should be covered. Protective clothing and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination from outside the clean area.
- *Grade C.* The hair and, where relevant, beard and moustache should be covered. A one-piece jumpsuit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes should be worn. The clothing should shed virtually no fibres or particulate matter.
- *Grades A and B.* Entry of personnel into grade A areas should be minimized. Headgear should totally enclose the hair and, where relevant, beard and moustache. A one-piece jumpsuit, gathered at the wrists and

with a high neck, should be worn. The headgear should be tucked into the neck of the suit. A facemask should be worn to prevent the shedding of droplets. Sterilized, non-powdered gloves of appropriate material and sterilized or disinfected footwear should be worn. Trouser-bottoms should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and should retain particles shed by the body.

10.9 Clothing used in clean areas should be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilization, there may be an increased risk of shedding particles. Washing and sterilization operations should follow standard operating procedures.

11. Premises

11.1 All premises should as far as possible be designed to avoid the unnecessary entry of supervisory or control personnel. Grade A and B areas should be designed so that all operations can be observed from outside.

11.2 In clean areas all exposed surfaces should be smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.

11.3 To reduce the accumulation of dust and to facilitate cleaning, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be carefully designed to avoid uncleanable recesses; sliding doors may be undesirable for this reason. Swing doors should open to the high-pressure side and be provided with self-closers. Exceptions are permitted based on egress and site environmental, health and safety containment requirements.

11.4 False ceilings should be sealed to prevent contamination from the void space above them.

11.5 Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Sanitary pipes and fittings should be used and threaded pipe connections should be avoided.

11.6 Sinks and drains should be avoided wherever possible and should be excluded from grade A and B areas where aseptic operations are carried out. Where installed they should be designed, located and maintained so as to minimize the risks of microbial contamination; they should be fitted with

effective, easily cleanable traps and with air breaks to prevent backflow. Any floor channels should be open and easily cleanable and be connected to drains outside the area in a manner that prevents the ingress of microbial contaminants.

11.7 Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand-washing facilities should be provided only in the first stage of the changing rooms.

There should not be a change of more than one grade between airlocks or passages and changing rooms, i.e. a grade D passage can lead to a grade C airlock, which leads to a grade B changing room, which leads to a grade B clean room. Changing rooms should be of a sufficient size to allow for ease of changing. Changing rooms should be equipped with mirrors so that personnel can confirm the correct fit of garments before leaving the changing room.

11.8 Airlock doors should not be opened simultaneously. An interlocking system and a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

11.9 A filtered air supply should be used to maintain a positive pressure and an airflow relative to surrounding areas of a lower grade under all operational conditions; it should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of approximately 10–15 Pascals (guidance value). Particular attention should be paid to the protection of the zone of greatest risk, i.e. the immediate environment to which the product and the cleaned components in contact with it are exposed. The recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain certain materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. The decontamination of the facilities and the treatment of air leaving a clean area may be necessary for some operations.

11.10 It should be demonstrated that airflow patterns do not present a contamination risk; for example, care should be taken to ensure that particles from a particle-generating person, operation or machine are not conveyed to a zone of higher product risk.

11.11 A warning system should be operated to indicate failure in the air supply. Indicators of pressure differentials should be fitted between areas

where this difference is important, and the pressure differentials should be regularly recorded and failure alarmed.

11.12 Consideration should be given to restricting unnecessary access to critical filling areas, e.g. grade A filling zones, by means of a physical barrier.

12. **Equipment**

12.1 A conveyor belt should not pass through a partition between a grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized (e.g. in a sterilizing tunnel).

12.2 Whenever possible, equipment used for processing sterile products should be chosen so that it can be effectively sterilized by steam or dry heat or other methods.

12.3 As far as possible, equipment fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance should be re-sterilized after complete reassembly, wherever possible.

12.4 When equipment maintenance is carried out within a clean area, clean instruments and tools should be used and the area should be cleaned and disinfected again, where appropriate, before processing recommences, if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work.

12.5 All equipment such as sterilizers, air-handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved.

12.6 Water-treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Consideration should be given to including a testing programme in the maintenance of a water system. Water for injection should be produced, stored and distributed in a manner which prevents the growth of microorganisms, e.g. by constant circulation at a temperature above 70°C or not more than 4°C (10).

13. **Finishing of sterile products**

13.1 Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules, should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

13.2 The container closure system for aseptically filled vials is not fully integral until the aluminum cap has been crimped into place on the stoppered vial. Crimping of the cap should, therefore, be performed as soon as possible after stopper insertion.

13.3 As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction.

13.4 Vial capping can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a grade A air supply until the cap has been crimped.

13.5 Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimize microbial contamination.

13.6 Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimizing direct human interventions into the capping operation.

13.7 Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, predetermined period.

13.8 Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is carried out visually this should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eyesight checks, using personal corrective lenses (e.g. spectacles or contact lenses) as required, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

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WHO GUIDELINE ON QUALITY RISK MANAGEMENT

This guideline has been prepared by Dr Simon Mills, United Kingdom.

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1. INTRODUCTION

1.1 Background and scope

In most countries compliance with good manufacturing practices (GMP) (1,2) (including validation), drug regulatory activities and inspections together provide good assurance that risks are largely controlled. However, in countries where control is less effective, patients may be put at risk through the production of drugs of inadequate quality. The assessment of individual risks related to specific products and starting materials and the recognition of hazards at specific stages of production or distribution should permit regulatory authorities to improve control of medicines by increasing the effectiveness of their activities within the limits of the available resources.

Hazard analysis and critical control point (HACCP) methodology, traditionally a food safety management system but subsequently applied to other industries, has been the basis of WHO risk management (RM) guidance to the pharmaceutical industry (3). The aim has been to assist the development and implementation of effective RM plans covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing and distribution. HACCP is science-based and systematic and identifies specific hazards and measures for their control, as well as providing information on environmental protection and labour safety. HACCP is a tool to assess hazards and establish control systems that focus on prevention rather than relying on corrective action based on end-product testing. All HACCP systems are capable of accommodating changes, such as advances in equipment design and processing procedures or technological developments.

However, recent international guidance has emerged (2,5,8) that is of specific relevance to the pharmaceutical industry and which addresses the full scope of pharmaceutical industry RM more effectively than HACCP principles, including how to structure regulatory filings using a risk-based approach. Consequently, this WHO guideline has been developed as an update of WHO advice to the pharmaceutical industry, taking account of this new guidance.

International medicines regulatory authorities (MRAs) are encouraging pharmaceutical manufacturers to adopt a risk-based approach to the development of drug products. In return for using this approach, there are potential opportunities for both MRAs and pharmaceutical manufacturers (4) as summarized in the following sections.

- a) Quality risk management (QRM) principles can be applied to both MRAs and pharmaceutical manufacturers and MRAs
 - MRAs: systematic and structured planning of reviews and inspections. The submission review and inspection programmes can also operate in a coordinated and synergistic manner.
 - Manufacturers: development, manufacture, distribution of medicines. RM can be an integral element of organizational culture.
- b) Science-based decision-making can be embedded into practice
 - MRAs: company decisions easier to scrutinize. Acceptance of residual risks through understanding the RM decisions involved.
 - Manufacturers: quality decisions and filing commitments can be based on science-based process understanding and RM (quality by design). Process control focused on critical attributes. Uncertainty can be addressed explicitly.

- c) Resources can be focused on risks to patients
- MRAs: RM can be used to determine best allocation of inspection resource, both in terms of product types and for specific areas of focus for a given inspection. This enables the most efficient and effective scrutiny of the most significant health risks. Those manufacturers with poor histories of GMP compliance can also be more closely and frequently evaluated by on-site inspection than those manufacturers with better records.
 - Manufacturers: evaluation of quality risk through science-based decisions can be linked ultimately to protection of the patient. Supports a corporate culture to focus on the patient as a primary stakeholder in all activities.
- d) Restrictive and unnecessary practices can be avoided
- MRAs: regulatory scrutiny adjusted to level of process understanding. Improvement and innovation by manufacturers is encouraged.
 - Manufacturers: instead of having systems designed to inhibit change and minimize business risk, changes can be managed within a company's quality management system. Real-time batch release is feasible. Innovation and the adoption of latest scientific advances in manufacturing and technology are supported.
- e) Communication and transparency are facilitated
- MRAs: facilitated dialogue with pharmaceutical manufacturers and tailoring of the inspection programme. Improved clarity of a company's decision-making process and judgement on critical issues.
 - Manufacturers: matrix team approach, stakeholders kept informed via science-based decisions. Culture of trust and "one-team" mindset with focus on product and patient.

QRM is the overall and continuing process of minimizing risks to product quality throughout its life-cycle in order to optimize its benefit/risk balance. It is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively. QRM should ensure the evaluation of risk to quality based on scientific knowledge and experience that ultimately links to the protection of the patient.

This guideline will align with the general framework described within other current international papers on this subject.

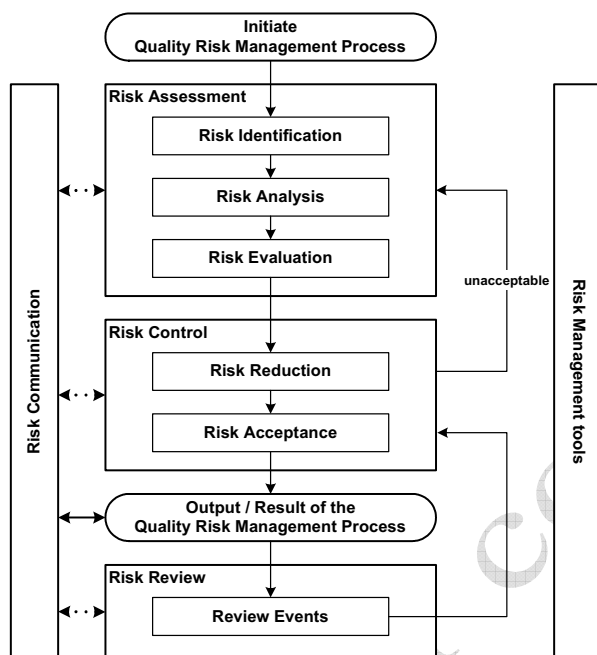
1.2 Principles of quality risk management

Four primary principles of QRM are:

- the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient;
- QRM should be dynamic, iterative and responsive to change;
- the level of effort, formality and documentation of the QRM process should be commensurate with the level of risk; and
- the capability for continual improvement and enhancement should be embedded in the QRM process.

This guidance describes the WHO approach to RM, using the concepts described in ICH Q9 and illustrated in Figure 1 (reproduced from ICH Q9). Other RM models could be used instead. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure 1. Overview of a typical quality risk management process



Taken from reference 5: ICH Q9: Quality Risk Management. This figure is also available on the ICH website www.ich.org.

Decision points are not shown in the diagram above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision. Note: “unacceptable” in the flowchart does not only refer to statutory, legislative or regulatory requirements, but also indicates that the risk assessment process should be revisited.

The approach described in this guideline should be used to:

- systematically analyse products and processes to ensure the best scientific rationale is in place to improve the probability of success;
- identify important knowledge gaps associated with processes that need to be understood to properly identify risks;
- provide a communication process that will best interface with all relevant parties involved in the RM plan;

- facilitate the transfer of process knowledge and product development history to ease product progression and to supplement generic corporate knowledge; and
- enable the pharmaceutical industry to adopt a risk-based approach to development as described in external regulatory guidance (5-8). The RM outputs will potentially serve as reference documents to support product development and control strategy discussions in regulatory filings.

Early in development, the purpose of the RM process is to manage risks and knowledge gaps associated with formulation development of the finished pharmaceutical product (FPP) according to the pharmaceutical product target profile (PPTP). In recognizing risks and knowledge gaps, the RM process plays a significant role in proactively enabling the prioritization and mitigation of risks. The objective is to develop the FPP through risk mitigation and the closing of knowledge gaps.

As FPP development progresses, in addition to supporting that development, the purpose of the RM process is to determine and manage risks to bioavailability, safety, efficacy and product quality from processing parameters and attributes. QRM in development should differentiate quality process parameters (QPPs) and quality attributes (QAs) from quality critical process parameters (QCPPs) and critical quality attributes (CQAs), respectively so contributing to the defining and refining of the control strategy.

The long process of product development is inevitably complex and requires the continual exchange of data, decisions and updates both internally within companies and externally with external stakeholders such as MRAs. A very important aspect of product development and QRM is the maintenance of an effective and secure knowledge management and documentation system. Such a system must facilitate transparent communication and the highlighting of key issues to stakeholders and also possess a well-structured archive. Clearly, the ability to organize diverse data and information effectively and then retrieve it as required for updating and further evaluation, for the purposes of process validation as an example, would be hugely beneficial.

Finally, it should be noted that QRM plans are focused on the process of product development, ultimately to ensure a robust and safe FPP. The existence and effectiveness of good clinical practices (GCP), good laboratory practices (GLP) and GMP should also be assessed when drawing up QRM plans.

2. QRM CONSIDERATIONS FOR MEDICINES REGULATORY AUTHORITIES (2,9)

2.1 Assessment of dossiers - inspection strategy

It is a requirement that regulatory inspections cover the QRM process of the organization in question. QRM, along with GMP and quality control (QC), should be considered as a key pillar of what must be a comprehensively designed and correctly implemented system of quality assurance (QA).

2.1.1 QRM system

All manufacturing authorization holders, developing countries' manufacturing sites and API manufacturers must have a system for QRM. Inspectors will review the QRM system as part of the quality systems section of the inspection (along with complaints, recalls, deviations, product quality reviews, etc.). Additionally, inspectors may review specific risk assessments when encountered during the course of an inspection. Inspectors can allocate time and resources commensurate with their perceived significance of the risk and, only if necessary, request the organization to produce a formal summary of the risk assessment, key decisions and conclusions or take risk-assessment details for further evaluation outside the inspection. Inspectors should be pragmatic regarding the level of scrutiny and degree of formality required for any given situation.

2.1.2 Standard operating procedures

The inspected organization must have a standard operating procedure (SOP) integrated with its quality system that defines how the management system operates and its general approach to both planned and unplanned risk assessment. It should include scope, responsibilities, controls, approvals, management systems, applicability and exclusions.

2.1.3 QRM deficiencies

As with other areas of inspection, deficiencies will be categorized dependent on the significance of the findings. Typically, the complete lack of a system should be classed as a major deficiency, while lesser deviations within a system would be classed as other. Critical deficiencies may reference QRM where risk assessments have inappropriately supported release of products that pose a threat to patient safety. QRM deficiencies may be grouped with other quality systems deficiencies under a quality systems heading, with factual statements clearly recording what are seen as deficiencies.

2.2 Inspection activities

Inspectors should expect inspected companies to demonstrate that appropriate skill, scientific knowledge, local knowledge and accountabilities were appropriate for the QRM procedure being inspected. This might be of particular relevance and concern where a company has made use of consultants and contractors. The following sub-sections provide inspection guidance in highlighting typical areas for scrutiny.

2.2.1 Inspection of a QRM system (11)

a) Integration of QRM into the company's quality management system:

- the areas of application of QRM should be appropriately defined in the company quality management system;
- there should be an appropriate number of personnel with relevant qualifications, experience and training. Their responsibilities should be clearly defined;
- senior management should be involved in the identification and implementation of QRM principles within the company;
- the risk management procedures for each area of application should be clearly defined;
- general QA standards should be applied to QRM-related documentation; and

- there should be clear evidence of sufficient resources being available to execute a company's QRM activities.

b) RM procedures:

- the workflow in relation to QRM activities should be systematic and conducted in a logical order. Those relevant to the inspection should be complete;
- there must be a clear overriding impression and evidence that all RM procedures are oriented towards patient safety. The procedures for risk-based decisions and formality of approach should be commensurate with the level of patient risk;
- there should be a logical approach to selection of methods and tools supporting a company's RM activities;
- the procedure for definition of risk acceptance criteria must be adequate, for example, involving personnel having appropriate expertise to understand all aspects of the evaluation;
- risk assessments must not underrate the likelihood, consequences or detection of occurrences such that the patient risk is underestimated. Consider challenging the factual evidence behind statements; and
- if the financial impact on the inspected organization is reported as a potential impact in a risk assessment, it must be ensured that this is not to the detriment of the patient.

2.2.2 Inspection of individual risk-based decisions (11)

(a) QRM system:

- the documented internal QRM and quality system procedures must be adhered to.

(b) RM activity:

- the risk question/problem should have been clearly defined;
- the people involved in the RM activity should have been suitably qualified and the team in combination should have appropriate expertise to address the question/problem defined;
- all relevant stakeholders should have participated at an appropriate level in the RM procedure;
- there should be a logical approach to selection of methods and tools supporting the risk-based evaluation and a systematic approach applied to prosecution of the RM activities;
- the key risks should have been adequately identified and analysed, with all relevant data having been generated and/or considered. All data reviewed must be from a reliable database. The risk acceptance criteria must be adequate for the specific situation in question;
- the risk-based decision(s) must be considered to be well-informed, science-based and comprehensible. They must be concordant with the pre-set acceptance criteria;
- the level of effort and reaction time invested in the RM activity should be proportionate to the importance of the identified problem. Critical issues should have been addressed with appropriate high urgency and formality and risk-based decisions made by staff with appropriate authority;

- the risk-reduction measures resulting from risk-based evaluations and decision(s) must demonstrate the required effect. The company should have adopted a suitable review programme to evaluate the outcome of the measures; and
- all documentation related to the RM activities should have been completed in a reasonable time frame and should be accessible to relevant staff and traceable at the time of inspection.

3. QRM AND PHARMACEUTICAL MANUFACTURERS

3.1 Training and education

As QRM is a relatively new concept in the pharmaceutical industry, training of personnel in industry, government and universities in QRM principles and applications is essential for its effective implementation. Industry employees must understand what QRM is, learn the skills necessary to make it function properly, and must also be given the materials and equipment necessary to enable the effective practice of the QRM principles and prosecution of product-specific plans.

In developing the training programme to support a particular QRM plan, working instructions and procedures should be drawn up which clarify the strategy and define the tasks of all involved in the plan. Specific training should be provided as required to enhance awareness. Staff who have responsibility for managing and reviewing risks must receive formal training in the relevant procedures.

Cooperation between producers, traders and responsible authorities is of vital importance. Opportunities should be provided for the joint training of industrial staff and control authorities to encourage and maintain a continuous dialogue and create a climate of understanding in the practical application of QRM.

The success of a QRM system depends on educating and training management and employees in the importance of their role in producing safe pharmaceuticals. Information should also be provided on the control of hazards at all stages of production and supply.

3.2 Responsibilities

Successful implementation of a QRM plan is dependent on a clear understanding of responsibilities for all staff involved in the plan as it progresses. It is recommended that a cross-functional matrix of assigned responsibilities and accountabilities is drawn up and shared with all relevant personnel. For a more complete picture of the communication pathways, the drafting of a RACI (Responsibility/Accountability/Consulted/Informed) grid should be considered.

The pharmaceutical manufacturer should assure that product-specific knowledge and expertise are available for the development of an effective QRM plan. QRM activities are usually, but not always, undertaken by a matrix of interdisciplinary teams. When teams are formed they should include experts from the appropriate areas (e.g. quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical) in addition to individuals who are knowledgeable about the QRM process.

In this respect it is acceptable for external consultants to participate in the QRM matrix team where they can provide specific expertise or knowledge. Their role should be justifiable and clearly defined and resultant accountability must be understood. A technical agreement with the consultant may be appropriate where a GMP responsibility is assumed.

Similarly, contract staff may become involved to lead or participate in risk assessments, e.g. a contract qualified person (QP). The extent of involvement and responsibility/accountability must be documented in a technical agreement between the individual and the pharmaceutical company. Regarding QPs, it is important that a company's internal procedures are clear on where the responsibility lies for final approval of risk acceptance documents.

Effective matrix team leadership is required to take responsibility for coordinating QRM across various functions and departments of their organization and ensuring that the QRM plan is defined, resourced, deployed and reviewed. The leader and team will need to identify critical resources to progress the QRM plan, and also specify a timeline, deliverables and appropriate levels of decision-making for the RM process.

3.3 Initiating a QRM process

A QRM plan should include systematic processes designed to coordinate, facilitate and improve science-based decision-making with respect to risk. Possible steps used to initiate and plan a QRM process might include the following (3).

3.3.1 Assemble a QRM team

The pharmaceutical manufacturer should assure that product-specific knowledge and expertise are available for the development of an effective QRM plan. This may be best accomplished by assembling a multidisciplinary team according to guidance in section 3.2.

Team members should be able to:

- (a) conduct a hazard analysis;
- (b) identify potential hazards;
- (c) identify hazards which should be controlled;
- (d) recommend controls and critical limits;
- (e) devise procedures for monitoring and verification;
- (f) recommend appropriate corrective action where deviations occur; and
- (g) verify the QRM plan.

The scope of the QRM plan should be defined. The scope should describe the segment of the process involved and the classes of hazards to be addressed should be identified.

3.3.2 Define the product and process

A full description of the product and the process should be drawn up, including relevant quality information such as the composition, physical/chemical properties, structure, pH, temperatures, method of cleaning, bactericidal/ bacteriostatic treatments (e.g. heat-treatment), drying, screening, mixing, blending, packaging and the storage conditions. The method of distribution and transport should also be described, especially where products are thermolabile.

3.3.3 Identify the intended use of the product

The intended use of the product (API and/or FPP) should be based on the expected uses of the product by the end-user or consumer. In specific cases, vulnerable population groups, e.g. geriatric patients, infants and immunocompromised patients, may have to be considered.

3.3.4 Construct and confirm a flow diagram

A flow diagram should be constructed by the QRM team, covering all operations and decisions in the process under development. When applying QRM to a given operation, the steps preceding and following that operation should also be considered. A block-type diagram may be sufficiently descriptive. The QRM team should then confirm the processing operation against the flow diagram during all stages and hours of operation. Amendments to the flow diagram may be made where appropriate, and should be documented.

3.4 Risk assessment (3)

When hazard identification and risk analysis is conducted safety concerns must be distinguished from quality concerns.

The QRM team should list all the hazards that may be reasonably expected to occur at each step from production, testing and distribution up to the point of use. It should then conduct a hazard analysis to identify for the QRM plan which hazards are of such a nature that their elimination or reduction to acceptable levels is essential.

A thorough risk analysis is required to ensure an effective control point. A two-stage risk analysis is recommended. During the first stage, the team should review the materials, activities, equipment, storage, distribution and intended use of the product. A list of the potential hazards (biological, chemical and physical) which may be introduced, increased or controlled in each step should be drawn up. In the subsequent risk analysis the following basic questions should be addressed:

- What is the nature of possible hazards?
- What is the probability of their occurrence and how easy is it to detect them?
- What are the consequences (the severity)?

The QRM team should then decide which potential hazards should be addressed in the QRM plan and what control measures, if any, exist that can be applied for each hazard. If a hazard has been identified at a step where control is necessary for safety, and no control measure exists at that step or any other, the product or process should be modified at that step, or at an earlier or later stage, to include such a control measure. More than one control measure may be required to control a specific hazard and more than one hazard may be controlled by a specified control measure.

This activity can be facilitated by the use of a decision-tree, which facilitates a logical approach. The way that a decision-tree is used will depend on the operation concerned, e.g. production, packing, reprocessing, storage or distribution. The best use of RM tools is discussed further in section 4 of this guidance.

Potential hazards in relation to at least the following should be considered:

- materials and ingredients;
- physical characteristics and composition of the product;
- processing procedures;
- microbial limits, where applicable;
- premises;
- equipment;
- packaging;
- sanitation and hygiene;
- personnel – human error; and
- risk of explosions.

The output of a risk assessment is either a quantitative estimate of risk (numeric probability) or a qualitative description of a range of risk (e.g. high/medium/low) and may be related to a risk matrix (see section 4). The scoring system and trigger points for mitigating action are subjective so the rationale for score categorization should be defined in as much detail as possible. If supported by factual evidence it should be more obvious what mitigating action is required – the mitigating action is as important as the score assigned. Professional judgement should be used in interpretation of factual evidence but must be subject to justification.

The expectation of QRM is to assess risks to the medicinal product and patient and then manage both to an acceptable level. It is appropriate for companies to assess their control systems to implement the optimum controls to ensure product quality and patient safety. If this can be achieved in a more cost-effective manner whilst maintaining or reducing risk to the product and patient then this is acceptable (9). Inappropriate risk assessment and mitigation in order to achieve cost savings but which could be to the detriment of the patient must be avoided.

3.5 Risk control

Risk assessments should be controlled within a defined document management system.

Acceptance limits must be specified and verified, if possible, for each critical risk requiring control. More than one acceptance limit may sometimes be elaborated at a particular step. The criteria used often include measurements of temperature, time, moisture level, pH and sensory parameters, such as visual appearance and texture. Acceptance limits should be based upon scientific knowledge of the process.

If risk assessments are conducted to justify controls for an ongoing process then the assessments should be subject to change control and periodic review, e.g. line clearance risk assessment. Frequency of review should be appropriate for the nature of the process. Such risk assessments should be seen as living documents that are visible and subject to change as required.

Risk assessments that were conducted as one-off activities to assess a situation that will not recur need not be controlled in a “live” manner but must be documented, approved and retained, e.g. assessment of storage temperature excursion. Such one-off activities should be controlled as live documents if any conclusions are to be used in any future relevant situations, e.g. another storage temperature excursion. Ultimately these may then need to be reviewed in light of experience or developments.

3.6 Risk communication and documentation

Communication of the QRM process must include all key stakeholders. By ensuring that key stakeholders are engaged in both the data collection process for the risk assessment and the decision-making for risk control, the QRM team will ensure buy-in and support. The output of the QRM process and associated risk analysis justifying the approach should be documented and endorsed by the organization's quality unit. Additionally, this information should be communicated to stakeholders for their information and to ensure their support.

It is not necessary to issue a full report for every risk assessment; the level of effort, formality and documentation of the QRM process can be commensurate with the level of risk (2). An organization can be pragmatic regarding the degree of formality that is required; however, appropriate evidence of mitigating activities should be available and a written output must be retained. Increased formality and detail will be expected for more significant risk.

Regarding conclusions to a risk assessment the mitigation controls should minimize the likelihood of risk to patient safety to an acceptable level of assurance, on the understanding that no risk whatsoever is unlikely in reality. The degree of risk tolerated very much depends on the circumstances, the proximity to the patient and other controls that might follow the process being assessed before the product reaches the patient (2). It is expected that risk mitigation plans are identified and implemented where any risk to patient safety is posed. Companies should take the holistic view and be mindful that critical issues often arise where multiple failures in systems occur together so mitigation plans should be sufficiently robust to cover this scenario. Inspectors will assess if risk assessments underrate the likelihood, consequences or detection of occurrences such that the patient risk is underestimated. The factual evidence behind statements must be robust to challenge by MRA inspectors.

All key risks within an organization should be listed in a register document for the purposes of inspection. This risk register (or equivalent title document) should list and track all key risks as perceived by the organization and summarize how these have been mitigated. There should be a clear reference to risk assessments and a list of risk assessments conducted should be included in or linked to the register. A management process should be in place to review RM – this may be incorporated into the quality management review process.

3.7 Risk control monitoring and review

Appropriate systems should be in place to ensure that the output of the QRM process is periodically monitored and reviewed, as appropriate, to assess new information that may impact on the original QRM decision. Examples of such changes include changes to control systems, changes to equipment and processes, changes in suppliers or contractors and organizational restructuring.

Monitoring is the scheduled measurement or observation of a specific risk control measure relative to its acceptance limits. Monitoring should be recorded.

The monitoring procedures used must be able to detect loss of control and this information should ideally be available in time to make adjustments to ensure control of the process and prevent violations of the acceptance limits. Where possible, process adjustments should be made when the monitoring results indicate a trend towards loss of control. These adjustments should be made before a deviation occurs.

Data derived from monitoring must be evaluated by a designated person with the knowledge and authority to carry out corrective actions when indicated.

If monitoring is not continuous, the amount or frequency of monitoring must be sufficient to guarantee that the risk is under control.

Most monitoring procedures for risk control measures will need to be done rapidly because they relate to online processes and there will not be time for lengthy analytical testing. For this reason physical and chemical measurements are often preferred to microbiological tests because they can be done rapidly and can often indicate the microbiological control of the product.

The personnel conducting the monitoring of risks and their control measures should be engaged in production (e.g. line supervisors, maintenance staff) and, where appropriate, QC staff. They should be trained in monitoring procedures.

Where continuous monitoring is possible a reliable monitoring procedure and frequency should be identified. Statistically designed data collection or sampling systems should then be used.

All records and documents associated with monitoring risks and their control measures must be signed and dated by the person(s) carrying out the monitoring and by a responsible reviewing official(s) of the company.

3.8 Establishment of corrective actions

Specific corrective actions should be developed for each risk in the QRM system in order to deal with deviations when they occur. These actions should ensure that the risk is brought under control. Corrective actions should include at least the following:

- (a) determination and correction of the cause of non-compliance;
- (b) determination of the disposition of the non-compliant product; and
- (c) recording of the corrective actions that have been taken.

Specific corrective actions should be developed in advance for each identified risk and included in the QRM plan. As a minimum this plan should specify what is to be done when a deviation occurs, who is responsible for implementing the corrective actions, and that a record will be kept and maintained of the actions taken. Individuals who have a thorough understanding of the process, product and QRM plan should be assigned the responsibility for the oversight of corrective actions.

As appropriate, experts may be consulted to review the information available and to assist in determining the disposition of non-compliant product. Actions taken must also include the proper disposition of the affected product.

Deviation and product disposition procedures must be documented in the QRM records.

3.9 Verification of a QRM plan (3)

The QRM plan that is put in place needs to be verified. Verification and auditing methods, procedures and tests, including random sampling and analysis, can be used to determine whether the QRM system is working correctly. The frequency of verification should be sufficient to confirm the proper functioning of the QRM system.

Examples of verification activities include:

- (a) review of the QRM system and its records;
- (b) review of deviations and product dispositions; and
- (c) confirmation that identified risks are kept under control.

Initial verification of the QRM plan is necessary to determine whether it is scientifically and technically sound, that all hazards have been identified and that, if the QRM plan is properly implemented, these hazards will be effectively controlled.

Information reviewed to verify the QRM plan should include:

- (a) expert advice and scientific studies; and
- (b) in-plant observations, measurements and evaluations.

Subsequent verifications should be performed and documented by a QRM team or an independent expert, as needed. For example, verifications may be conducted when there is an unexplained system failure, a significant change in product, process or packaging occurs or new hazards are recognized. Where possible verification should include actions to confirm the efficacy of all elements of the QRM plan.

In addition, a periodic comprehensive evaluation of the QRM system by an unbiased, independent third party is useful. This should include a technical evaluation of the hazard analysis and each element of the QRM plan as well as an on-site review of all flow diagrams and appropriate records of the operation of the plan. Such a comprehensive verification is independent of other verification procedures and must be performed in order to ensure that the QRM plan is resulting in the control of the hazards. If the results of the comprehensive verification identify deficiencies, the QRM team should modify the QRM plan as necessary.

Individuals doing verification should have appropriate technical expertise to perform this function.

3.10 Product development

The application of RM procedures evolves through the various stages in development of a product.

It is important to, where possible, identify risks in the early phases of product development that could challenge the achievement of the PPTP. The first RM exercise should be performed once the PPTP is defined and preformulation work on the drug candidate is complete. For this stage of a project there may be significant gaps in knowledge. Therefore, it will be important to apply risk tools that are appropriate for such a situation. These might include:

- cause and effect diagrams (also known as Ishikawa or Fishbone diagrams);
- flowcharts (e.g. input-process-output(IPO));
- decision-trees;
- fault-tree analysis; and
- relationship matrices.

As the product progresses to later stage development, a more detailed analysis of the risks associated with both the API and FPP becomes a requirement. Risks would cover concerns associated with stability, bioavailability and patient safety including any challenges to these

resulting from the manufacturing process (including, for example, API form conversion under certain conditions of processing).

As product knowledge advances more detailed RM exercises can be considered, concentrating on areas considered to be higher priority risk. As the product's critical quality attributes (CQAs) become defined, the potential risks arising from each input material (API, excipients, any device or pack components) and each secondary product unit operation can be investigated.

Eventually, for the developed FPP the increasingly comprehensive risk assessment will support a thorough understanding of the product and will enable all key variables to be identified, understood and controlled.

3.11 Validation and qualification

In keeping with the principles of QRM and risk-based pharmaceutical development, this guideline recommends that process validation embraces the product life cycle concept already mentioned. Accordingly, process validation activities should involve the generation and evaluation of data throughout the development process into full-scale production that will provide a science-based assurance of consistent delivery of quality product in the production operation. The current FDA draft process validation guidance reflects this approach (12). A European-based critique of the FDA guidance has also been issued (13).

An important emphasis is that the building of scientific assurance begins early in development. It is obtained through rational design of experiments and robust evaluation of data during product/process development through to the commercial production phase at which time the API and drug product CQAs are well understood and controlled. In this scenario, validation or (perhaps more appropriately termed) conformance batches just serve to reinforce the science- or risk-based decisions that have been made as product development has advanced and should demonstrate good control of all identified critical sources of variability. Any unplanned variations within a batch or between batches should be evaluated accordingly, employing suitable statistical tools, e.g. trend analysis, to check on process control.

A potential advantage of this approach is that there can be flexibility in the number of validation or conformance batches required for regulatory scrutiny prior to approval. The traditional number of batches required for validation has been three but, with QRM embedded in a product's development process, the number of conformance batches that needs to be made depends on the depth of knowledge about the process. For very low-volume products, e.g. orphan drugs, this may preclude the need to manufacture unneeded batches. Clearly, for all decisions of this nature regarding conformance batches, it will be very important to have an effective company/MRA dialogue to agree on requirements for a regulatory submission.

Most importantly, by the time that a product is ready for commercialization, the manufacturing company will be expected to have derived sufficient knowledge of the commercial production process to support that commercialization to the optimized benefit of and minimized risk to the patient.

4. RISK MANAGEMENT TOOLS

A variety of tools can be used for the purposes of QRM, either alone or in combination. It is important to note that no single tool or combination of tools is applicable to every situation in which a QRM procedure is used. Examples of tools are listed in regulatory guidance (6,8); neither list is exhaustive. The important criterion for acceptability is that the tool or tools are used effectively to support the key attributes of a good risk assessment.

The Product Quality Research Institute (PQRI) Manufacturing Technology Committee (MTC) has produced a summary (10) of common RM principles and best practices, several working tools to foster consistency in the use of ICH Q9 (6) in day-to-day RM decision-making, and a series of examples of RM applications currently in use by major pharmaceutical firms. They have also produced very helpful risk tool training modules for risk ranking and filtering, failure modes effects analysis (FMEA), hazard operability analysis (HAZOP) and HACCP (10). As an element of the WHO guidance on QRM, this PQRI report is recommended as a training resource and to gain an understanding into how best to use RM tools.

One aspect worth highlighting is the development of a risk matrix to facilitate categorization of identified risks during the risk assessment phase. In order to prioritize a risk, it is essential to agree upon its significance. The risk associated with any situation or event can be represented as the impact of that event multiplied by the probability of its occurrence; in other words, how likely is it to happen and how severe would it be if it did happen. Impact and probability can each be classified, e.g. into 5 levels (1-5), so that a grid or matrix can be constructed.

Table 1. Probability versus impact matrix

Probability	Impact				
	Negligible	Marginal	Moderate	Critical	Catastrophic
Almost certain	5	10	15	20	25
Likely	4	8	12	16	20
Possible	3	6	9	12	15
Unlikely	2	4	6	8	10
Rare	1	2	3	4	5

The shading in the table represents an example of how the risk values (sometimes called composite risk indices or risk index values) can be assigned a high, medium or low status. The definition for each status should be predetermined by the QRM team after consideration of the specific consequences for the process undergoing risk assessment. These consequences can be split according to the probability and impact scores, as exemplified in Table 2.

Table 2. Example of a consequences table for probability and impact

Score	Probability	Example	Score	Impact	Consequence
1	Rare	Seen every 10-30 years	1	Negligible	- No regulatory issue - No effect on and not noticeable by patient
2	Unlikely	Seen every 5-10 years	2	Marginal	- May require MRA notification - Decision to release product not compromised
3	Possible	Seen every 1-5 years	3	Moderate	- MRA inspection may identify a major concern but deficiency quite easily resolved - Limited product recall possible
4	Likely	Seen to occur more than once a year	4	Critical	- MRA inspection may conclude serious non-compliance - Likely product recall from one or more markets
5	Almost certain	Seen several times a year	5	Catastrophic	- Enforcement action by MRA such as consent decree, product seizure - Global product recall

This table is just a very basic example and would need to be customised by a QRM team for the specific process in question to enable better and practical definition of the consequence categories. It should be cautioned that the value of a risk matrix does very much rely upon input information and should only be used by staff with a good understanding of the embedded judgements and, as such, the resolution of low/medium/high categorization.

As a summary of the common, well-recognized RM tool options available for the purposes of this guideline, the following table has been taken from the PQRI-MTC report¹⁰. The list is not comprehensive but it does include some of the more frequently used approaches.

Table 3. Common risk management tools (10)

Risk management tool	Description/attributes	Potential applications
Basic tools		
Diagram analysis • Flowcharts • Check sheets • Process mapping • Cause/effect diagrams	• Simple techniques that are commonly used to gather and organise data, structure RM processes and facilitate decision making	• Compilation of observations, trends or other empirical information to support a variety of less complex deviations, complaints, defaults or other circumstances
Risk ranking and filtering	• Method to compare and rank risks • Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and weighting factors and risk scores	• Prioritize operating areas or sites for audit/assessment • Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool
Advanced tools		
Fault tree analysis (FTA)	• Method used to identify all root causes of an assumed failure or problem • Used to evaluate system or sub-system failures one at a time, but can combine multiple causes of failure by identifying causal chains • Relies heavily on full process understanding to identify causal factors	• Investigate product complaints • Evaluate deviations
Hazard operability analysis (HAZOP)	• Tool assumes that risk events are caused by deviations from the design and operating intentions • Uses a systematic technique to help identify potential deviations from normal use or design intentions	• Access manufacturing processes, facilities and equipment • Commonly used to evaluate process safety hazards
Hazards analysis and critical control points (HACCP)	• Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring • Bottom-up approach that considers how to prevent hazards from occurring and/or propagating • Emphasises strength of preventative controls rather than ability to detect • Assumes comprehensive understanding of the process and that critical process parameters (CPPs) have been defined prior to initiating the assessment. Tool ensures that CPPs will be met.	• Better for preventative applications rather than reactive • Great precursor or complement to process validation • Assessment of the efficacy of CPPs and the ability to consistently execute them for any process (continued)

Risk management tool	Description/attributes	Potential applications
Advanced tools		
Failure modes effects analysis (FMEA)	- Assesses potential failure modes for processes, and the probable effect on outcomes and/or product performance - Once failure modes are known, risk reduction actions can be applied to eliminate, reduce, or control potential failures - Highly dependent upon strong understanding of product, process and/or facility under evaluation - Output is a relative “risk score” for each failure mode	Evaluate equipment and facilities; analyse a manufacturing process to identify high risk steps and/or critical parameters

[Note from the Secretariat: the authors will be contacted regarding copyright of this table.]

Another general overview of and references for some of the risk tools that might be brought to bear in QRM by industry and regulators is provided in Annex 20 (Annex I) of the EU GMP guideline (2).

5. GLOSSARY

Control strategy (source: ICH Q8)

A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and pharmaceutical product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (ICH Q10).

Critical quality attribute (CQA) (source: ICH Q8)

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Finished pharmaceutical product (FPP)

The finished pharmaceutical product always represents a pharmaceutical product after final release (manufacturing control release, quality control release, packaging control release).

Formal experimental design (source: ICH Q8)

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “design of experiments”.

Planned risk assessment

An assessment that is conducted in advance of an activity, either before any work is conducted or before further work is conducted. This enables quality to be built into activities and risk reduced, e.g. design of high containment facilities for manufacture of cytotoxic products.

Pharmaceutical product

Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Pharmaceutical product target profile (PPTP)

A definition of the target properties of the FPP, including dosage form and strength(s), route of administration and relevant drug release and pharmacokinetic requirements

Process robustness (source: ICH Q8)

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

Product quality research institute (PQRI)

A collaborative process involving the United States Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER), Industry, and Academia. The mission of PQRI is to conduct research to generate specific scientific information that should be submitted in a regulatory filing to CDER (but which will be worth consideration for all MRAs). PQRI member organizations, representing industry, academia, and government, cover a wide array of scientific issues related to pharmaceutical products. Through its working groups and technical committees, PQRI tackles projects to ensure the quality, safety and performance of drug products and produces publications for the public domain based upon the output of those projects.

Quality critical process parameter (source: ICH Q8)

A process parameter whose variability has an impact on a critical quality attribute and, therefore, should be monitored or controlled to ensure the process produces the desired quality.

Stakeholder

Any individual, group or organisation that can affect, be affected by, or perceive itself to be affected by a risk. Primary stakeholders are the patient, healthcare professional, MRAs and the pharmaceutical industry.

Unplanned risk assessment

An assessment that is conducted to assess the impact of a situation that has already occurred, e.g. impact of a deviation from normal ways of working.

Validation

The collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes- including equipment, buildings, personnel and materials are capable of achieving the intended results on a consistent and continuous basis. Validation is the establishment of documented evidence that a system does what it is supposed to do.

Verification

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with the risk management plan.

6. REFERENCES

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ANNEXES

(Examples of QRM application to be added)

[Note from the Secretariat: contributions with examples would be much appreciated.]

Draft for comment



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 October 2010
EMA/INS/GMP/638479/2010
GMP/GDP IWG

Concept paper on storage conditions during transport

Agreed by GMP/GDP Inspectors Working Group	March 2010
Agreed by QWP	May 2010
BWP consulted	September 2010
Agreement by GMP/GDP IWG for release for consultation	September 2010
End of consultation (deadline for comments)	28 February 2011

The proposal will create new GDP and GMP guidance and may lead to the need to revise guideline: CPMP/QWP/609/96/Rev2 – 'Guideline on Declaration of Storage Conditions: A: In the Product Information of Medicinal Products B: For Active Substances' and other relevant guidance including veterinary guidance

Comments should be provided using this [template](#). The completed comments form should be sent to ADM-GMDP@ema.europa.eu



1. Introduction

The globalisation of the manufacture of human and veterinary medicinal products has brought both benefits and a wide range of challenges. This paper is concerned with challenges related to the maintenance of appropriate transit conditions during transport as products move through all stages of the manufacturing and wholesale distribution system from active substance through the wholesale distribution system to ensure that patients and animals receive safe and efficacious medicinal products. The current guidance (CPMP/QWP/609/96/Rev2) was written in 1996 and revised in 2003, during this time significant changes continued to occur in the globalisation of manufacture with a consequent increase in the complexity and vulnerability in the supply chain.

2. Problem statement

There is a lack of clear guidance on the regulatory expectations for ensuring that medicinal products and APIs are not damaged during transportation. In order that products are fit for their intended purpose, including the ability to tolerate the range of expected storage conditions during use by patients or use in animals, simple and risk-based guidance is required for the transport. Such guidance needs to cover cold chain and non-cold chain products and all of the different stages of manufacture, importation and distribution.

3. Discussion

From a product's perspective, transport is a mobile form of storage but where there are weaker controls than storage in fixed sites – therefore similar levels of controls should exist. Compliance at all stages of manufacture and distribution becomes more important as the number of transport stages increase, including transport (i.e. import) into the EU. Several examples have been seen where sea-freight significantly exceeds 30 days. Any increases in the length of time and/or the climatic challenge at each stage will also impact on compliance. It is also increasingly difficult to be aware of and to assess the cumulative effects of adverse incidents at different stages.

Many sites of manufacture are now located in tropical zones and/or where transport infrastructure may be difficult. Therefore the challenges arising from transport between such sites and from these sites to the EU may take finished products, or their earlier stages of manufacture, outside of the conditions defined in the EU Marketing Authorisation for storage of the product. Also, the risk of freezing during transport and the effects on the products should be considered.

It is important to understand the susceptibility of different products at the different stages and whilst the principles of quality risk management would be applied on a product by product basis at each stage of manufacture and transport would be expected, the reality is that different products and different product stages are frequently co-shipped. It is therefore evident that a simple set of readily understood general rules should apply to transit conditions to reduce this complexity and risk of error. Although widely acknowledged, there is no explicit requirement for the need to conduct transport studies under worst case conditions and no requirement for routine monitoring during transport.

4. Recommendation

Whilst aligning, where possible, requirements with other key guidance documents (e.g. WHO, USP), the following are recommended:

1. Conduct the procedure by a linked parallel process under QWP, BWP and GMP/GDP IWG.
2. Consider the need to revise the QWP guidance.
3. Align with the text in the GDP guidance (under revision) and GMP Chapters 5, 6 and 7, Annex 15 (all currently under revision), Annex 16 and create new FAQs.

5. Proposed timetable

Approval of Concept Paper by GMP/GDP IWG in March, by QWP in May 2010 and by BWP in September 2010.

Release the Concept Paper for a 3 month consultation in October 2010, deadline for comments by January 2011. Produce initial GMP Q&As.

Review comments and revise relevant texts for initial discussion at QWP, BWP and GMP/GDP IWG by February 2010.

GMP/GDP IWG - Release draft text in June 2011 for 3 month consultation, deadline for comments September 2011.

- Re-discussion and agreement at GMP/GDP IWG November 2011. Finalise Q&As.

QWP/BWP - The need for new or revised complementary guidance falling under the responsibility of QWP or BWP will be subject to specific Concept Papers with their own timelines as needed.

6. Resource requirements for preparation

There will be 1 rapporteur for each of GMP/GDP IWG and QWP, documents will be submitted to 2 working party meetings, 2 drafting group meetings are anticipated.

7. Impact assessment

It is anticipated that public and animal health will benefit by the maintenance of the assurance of the quality of products with continued globalisation in manufacture. For industry and regulatory authorities there will be greater clarity in the transport condition requirements. There will be no net increase in resource requirements for regulatory authorities. It is likely that there will be some alteration to some types of transport currently used and some additional costs for monitoring shipments.

8. Interested parties

EMA – GMP/GDP IWG, QWP, BWP.

Industry – manufacturers and brokers of API, bulk and finished products, Transport service providers and logistics providers

9. References to literature, guidelines

1. CPMP/QWP/609/96/Rev2 – 'Guideline on Declaration of Storage Conditions: A: In the Product Information of Medicinal Products B: For Active Substances
2. World Health Organization – 'Proposal For Revision of WHO Good Distribution Practices for Pharmaceutical Products'.
3. USP 1079 "Good Storage and Shipping Practices".

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Guidance for Industry and FDA Staff:

Early Development Considerations for Innovative Combination Products

For questions regarding this document, contact:
Patricia Y. Love, MD, Office of Combination Products, at 301-427-1934.

**U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner
Office of Combination Products**

September 2006

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Guidance for Industry and FDA Staff

Early Development Considerations for Innovative Combination Products

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**U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner
Office of Combination Products (OCP)
September 2006**

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Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Guidance for Industry and FDA Staff¹

Early Development Considerations for Innovative Combination Products

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document provides guidance to industry and FDA staff on developmental considerations for innovative products that combine devices, drugs and/or biological products. It is intended to provide a context for initial discussions on the type of scientific and technical information that may be necessary for investigational or marketing applications for these combination products.

This guidance focuses on combination products as defined under 21 CFR 3.2(e). The concepts may also be useful for the co-development of devices, drugs, and biological products that are used concomitantly but which do not meet the regulatory definition of a combination product.

This information supplements existing guidance documents developed by the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Office of Combination Products (OCP).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

¹ This guidance has been prepared by the Center for Devices and Radiological Health, the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Office of Combination Products in the Office of the Commissioner at the Food and Drug Administration.

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II. BACKGROUND

FDA recognizes that innovative technologies may raise a spectrum of scientific and technical development issues. Combination products are increasingly incorporating cutting edge, novel technologies that hold great promise for advancing patient care. Innovative drug, biological product, device combinations have the potential to make treatments safer, more effective, or more convenient or acceptable to patients. For example, drug-eluting cardiovascular stents may reduce the need for repeated surgery by helping to prevent the restenosis that may occur after stent implantation. Drug and biologic products can be used in combination to potentially enhance the safety and/or effectiveness of either product used alone. Proteins incorporated into novel orthopedic implants may facilitate the regeneration of bone required to permanently stabilize the implants. Drug-device inhalation systems provide a new route of insulin delivery that may decrease the need for insulin injections. Genomic-based diagnostic devices may be used to help determine whether certain patients are suitable candidates for a drug or biological product, or at risk for certain types of adverse events.²

During an FDA workshop entitled, “*Innovative Systems for Delivery of Drugs and Biologics: Scientific, Clinical and Regulatory Challenges*,” industry and academic stakeholders requested that FDA provide guidance for the development of innovative technology that may challenge existing approaches.³ For example, what pre-clinical or animal studies are appropriate to begin human studies, or what types of clinical trial designs may be appropriate? Further, FDA recognizes that combination product development may raise a number of Critical Path⁴ challenges to progress from a novel concept to an innovative marketed product.

Some of these developmental challenges may not be readily apparent. For example, although a combination product may be comprised of an already approved drug and an already approved device, new scientific and technical issues may emerge when the drug and device are combined or used together. New methodologies may need to be developed for manufacturing, evaluation of preclinical safety in targeted areas of the body, or clinical trial design to establish safety and effectiveness.

FDA websites contain a wide variety of guidance documents for the development and testing of drugs, devices, and biological products. These address drugs, devices, or biological products as individual products, but few guidance documents currently address the scientific and technical issues to consider when combining drug, device, and/or biological product constituent parts as a combination product..

FDA believes it is important to address the scientific and technical issues raised by innovative combination products in order to develop efficient, appropriate techniques and methods to ensure the safety, effectiveness, and quality of the combination product.

² Drug-pharmacogenomic test pairings may be considered combination products, depending how the products are intended for use and labeled. FDA is developing separate guidance for the co-development of drug and genomic-based diagnostic devices, and these types of products are not specifically addressed in this document.

³ A summary of the workshop is available at <http://www.fda.gov/oc/combo/workshop070803.html>.

A transcript is available at <http://www.fda.gov/ohrms/dockets/dockets/03n0203/03n0203.htm>.

⁴ See *The Critical Path to New Medical Products* at <http://www.fda.gov/oc/initiatives/criticalpath/>.

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A. Definition

As defined in 21 CFR 3.2(e), a combination product is a product comprised of any combination of a drug and a device, a biological product and a device, a drug and a biological product, or a drug, device, and a biological product. This includes:

- “A product comprised of two or more regulated components; i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
- Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
- A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed; e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
- Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.”

For purposes of this guidance, a constituent part of a combination product is an article in a combination product that can be distinguished by its regulatory identity as a drug, device, or biological product, as defined in section 21 U.S.C. 321, Federal Food, Drug, and Cosmetic Act (Act), and 42 U.S.C. 252 (i), Public Health Service Act, and as set forth in 21 CFR 3.2(k). For example, a device coated or impregnated with a drug has two constituent parts, the device constituent and the drug constituent. For simplicity, the concepts in this guidance are described in the context of a combination product composed of two constituent parts. These concepts are also relevant for combination products with more than two constituent parts.

B. How are combination products regulated?

FDA’s Office of Combination Products (OCP) was established in 2002 as required by the Medical Device User Fee and Modernization Act of 2002. As set forth in section 503(g) of the Act, OCP is responsible for the prompt assignment of a lead Agency center that will have primary jurisdiction for the review and regulation of a combination product; ensuring timely and effective premarket review by overseeing the timeliness of and coordinating reviews involving more than one agency center; ensuring consistent and appropriate postmarket regulation of combination products; and resolving disputes regarding the timeliness of combination product

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review. OCP also works with agency centers to develop guidance and regulations to make the regulation of combination products as clear, consistent, and predictable as possible. Under section 503(g)(1) of the Act, a combination product is assigned to a center with primary jurisdiction, or a lead center, based on a determination of the primary mode of action (PMOA) of the combination product. PMOA is defined as “the single mode of action of a combination product that provides the most important therapeutic action of the combination product.” For example, if the PMOA of a device-biologic combination product were attributable to its biological product constituent, the Agency component responsible for premarket review of that biological product would have primary jurisdiction for the combination product. The final regulation also includes an assignment algorithm that the Agency will use when the most important therapeutic action of a combination product cannot be determined with reasonable certainty.⁵

A combination product is assigned to one of the Agency’s three human medical product Centers: CBER, CDER, or CDRH. The lead center has oversight responsibility for the review and regulation of the combination product. The lead center often consults or collaborates with other agency components and OCP, as appropriate, to identify and evaluate the information needed for a regulatory submission (e.g., investigational application or marketing authorization).

In streamlining the review of combination products, FDA established a Standard Operating Procedure for the Intercenter Consultative and Collaborative Review Process.⁶ The document provides the policies and procedures for FDA staff to follow when requesting, receiving, handling, processing, and tracking formal consultative and collaborative reviews of combination products, devices, drugs and biologics. The objectives of the SOP are to ensure timely and effective intercenter communication on combination products, as well as the timeliness and consistency of intercenter consultations and collaborations.

This guidance describes general information on developmental considerations for products that combine devices, drugs, and/or biological products. Although details on the regulatory processes described in this section are beyond the scope of this guidance document, FDA encourages developers to contact OCP for assistance in determining the assignment of a lead center when jurisdiction is unclear or in dispute, the number and type of marketing applications⁷, the

⁵ See final rule for *Definition of the Primary Mode of Action of a Combination Product*, published August 25, 2005, Federal Register, <http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.pdf>

⁶ See Intercenter *Consultative/Collaborative Review Process* at <http://www.fda.gov/oc/combination/consultative.html>.

⁷ For most combination products, a single marketing application is sufficient for the product’s approval, clearance or licensure. In some cases, however, a sponsor may choose to submit two marketing applications for a combination product when one application would suffice. For example, a sponsor may choose to submit two applications in order to receive some benefit that accrues only from approval under a particular type of application (e.g., new drug product exclusivity, orphan status, or proprietary data protection when two firms are involved). In other cases, FDA may determine that two marketing applications are necessary. For example, when one of the individual constituent parts of a combination product is already approved for another use, and where the labeling of the already approved product will need to be changed to reflect its new intended use in the combination product, FDA may determine that two applications are necessary if the labeling of the already approved product is subject to legal requirements different from those that will apply to the combination product. FDA encourages applicants who are uncertain as to whether a single or multiple marketing applications should be submitted for a combination product to discuss the issue with the lead reviewing Division and/or OCP. Information about the applicable time frames is provided in the

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premarket review process, and the postmarket regulations such as adverse event reporting or good manufacturing practice requirements that may be appropriate for a combination product. OCP will work with the agency Centers as appropriate to facilitate a response. Additional information on combination product regulation, guidance, and process is available on OCP's website.⁸

III. GENERAL DEVELOPMENT CONSIDERATIONS

As with other medical products, combination product development typically focuses on the scientific and technical issues raised by the particular product being developed. For a combination product, these scientific/technical issues will ordinarily reflect the combination product itself as well as its constituent parts. When combining products such as drugs or biologics and devices that are customarily developed using different regulatory paradigms, certain critical developmental issues, such as the interaction of the drug/biologic and device constituents, may not be readily apparent. Further, because of the breadth, innovation and complexity of combination products, there is no single developmental paradigm appropriate for all combination products.

Existing guidance documents are generally excellent starting points for considering the types of issues raised by the constituent parts of a combination product, but often they will need adaptation to fully address the combined nature of a combination product. For example, guidance for preclinical evaluation of drugs/biologics differs from the preclinical/non-clinical studies conducted for devices. When developing a combination product, it is likely that neither isolated approach would fully address the relevant preclinical development questions for both constituents as well as for the combination product as a whole. Instead, FDA recommends that developers consider the scientific and technical issues raised by the combination product and its constituents and propose an approach that appropriately addresses these issues without requiring duplicative or redundant studies.

In many circumstances, the development considerations depend on the type of combination product. When the combination product is comprised of constituents that are chemically, physically or otherwise combined or mixed and produced as a single entity, developers should consider and, as appropriate, evaluate the potential for a broad range of drug/biologic/device interactions. For example, for a drug eluting stent, the mechanical attributes of the polymer coating system that contains the drug substance are important for stent deployment, drug release, biocompatibility, and stability. For some combination products, the constituents may have synergistic effects that should be evaluated. In the context of these studies, it is appropriate to discuss approaches to avoid duplication/redundancy and to develop strategies to streamline the overlapping aspects of development.

Innovative new technology may also challenge existing approaches for product development. For example, a new device used to deliver a drug/biologic to a new area of the body that was

guidance document "Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product," available at <http://www.fda.gov/oc/combination/dispute.pdf>.

⁸ See OCP's website at <http://www.fda.gov/oc/combination>.

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previously inaccessible might make it necessary to develop new methods to determine the effect of such localized/targeted delivery, particularly when it results in higher exposure to that target than when the drug is systemically administered. Likewise, innovative technologies such as nanotechnology or live cellular products may lead to the development of new manufacturing methodologies or unique safety issues not associated with products manufactured in other ways.

The following sections describe general principles to consider when developing information to demonstrate the safety and effectiveness of a combination product and its constituent parts. We recommend that combination product developers particularly consider the preclinical and non-clinical testing that should be conducted for their product, and how such testing may be influenced by the interaction of the constituent parts, and any prior approval/clearance of a constituent part. FDA believes that the general principles described in this guidance document would assist developers in providing the appropriate data to help establish the safety and effectiveness of innovative combination products. Consideration of these issues in the context of existing guidance documents may lead to a more targeted and efficient development pathway for the combination product.

IV. CURRENTLY MARKETED PRODUCT CONSIDERATIONS

Prior FDA approval and/or clearance of a particular constituent part of a combination product is often an excellent starting point for considering the appropriate data to establish safety and effectiveness for its use in a combination product. FDA recommends that developers fully consider what is already established about a constituent part; i.e., what existing information and data are available, to avoid duplication and ensure a more timely and efficient development process. Throughout the development process, however, it is critical to recognize that it is the *combination product* that is being developed for approval/clearance, not just the constituent part. While this prior information is often very helpful, developers should recognize that additional data and information may be necessary to address the scientific and technical issues raised by the new use of the constituent in the combination product. These issues may be raised by combining the constituent parts or by new uses for the constituent in the combination product, such as a new indication for use, a different target population, a new route of administration, or by different local or systemic exposure profiles once the products are combined. For example, developers should consider:

- Are the constituent parts already approved for an indication?
- Is the indication for a given constituent part similar to that proposed for the combination product?
- Does the combination product broaden the indication or intended target population beyond that of the approved constituent part?
- Does the combination product expose the patient to a new route of administration or a new local or systemic exposure profile for an existing indication?
- Is the drug formulation different than that used in the already approved drug?
- Does the device design need to be modified for the new use?
- Is the device constituent used in an area of the body that is different than its existing approval?

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- Are the device and drug constituents chemically, physically, or otherwise combined into a single entity?
- Does the device function as a delivery system, a method to prepare a final dosage form, and/or does it provide active therapeutic benefit?
- Is there any other change in design or formulation that may affect the safety/effectiveness of any existing constituent part or the combination product as a whole?
- Is a marketed device being proposed for use with a drug constituent that is a new molecular entity?
- Is a marketed drug being proposed for use with a complex new device?

As illustrated in the following sections, FDA recommends that the developmental studies should take into account these questions as appropriate for the constituent parts alone and for the finished combination product. FDA furthermore recommends that these issues be considered in the context of the proposed indication.

V. PERSPECTIVES BY CONSTITUENT PART

A. Device constituent considerations

For new device constituent parts, some safety and/or effectiveness testing of the device alone may be necessary before or along with the studies to establish the safety and effectiveness of the combination product as a whole. For device constituent parts that are already approved/cleared for another purpose, the extent of preclinical testing largely would focus on the new use of the device constituent as part of the combination product. For example, if a combination product incorporates an indwelling, intravenous drug delivery catheter for a new use for long-term, drug delivery in the brain, new biocompatibility studies may be necessary to establish the safety of the device materials for placement in neural tissues. New engineering or functional testing may also be necessary to establish the suitability of the device design to the new environment in which it will be used.

Consideration should also be given to the potential interaction (desired or undesired) between the device and the drug/biological constituents. For example, it may be appropriate to conduct studies to evaluate the potential for the following:

- Leachables/extractables of the device materials into the drug/biologic substance or final combination product;
- Changes in stability of the drug constituent when delivered by the device or when used as a coating on the device;
- Drug adhesion/absorption to the device materials that could change the delivered dose;
- Presence of inactive breakdown products or manufacturing residues from device manufacture that may affect safety, or device actions that could change the drug performance characteristics at the time of use; or
- Changes in the stability or activity of a drug constituent when used together with an energy emitting device.

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Likewise, similar consideration should be given to the effects a drug or biological product may have on the device constituent. For example, the material properties of a delivery catheter may be adversely affected by some drug/biologic products but not others.

CDRH has an active program of evaluating and recognizing consensus standards.⁹ For many combination products, it may be appropriate to use these existing consensus standards for the device constituents of a combination product, including the standard test methods. For others, particularly those that are innovative, it may be appropriate to adapt these standards, or it may be necessary to develop new methodologies. Because of the range of combination products and developmental strategies, developers are encouraged to seek early discussions with FDA when exploring the application of standards to candidate constituent parts and when alternative methodologies or approaches are being developed.

B. Drug and biological product constituent considerations¹⁰

When a new molecular entity (NME) is a constituent part of a combination product, it is critical to consider what information is necessary to characterize the safety and effectiveness of the NME when used in the combination product. Generally this begins with a consideration of the NME alone; e.g., the preclinical information necessary to begin the initial studies in human subjects of the NME and the information needed for combination of the NME and the device constituent. For example, certain conventional pharmacology and toxicology studies may be necessary to establish the safety profile of the NME alone (e.g., genotoxicity, mutagenicity, immunotoxicity, and local tolerance) before beginning clinical investigation of the combination product.¹¹ It is also important to consider the timing to initiate any necessary reproductive and carcinogenicity studies; these types of studies are generally conducted after beginning the clinical investigation, and they are generally submitted in the marketing application for the product.

When the combination product contains a drug/biologic constituent that is already approved for another use, we recommend that the developer address the potential for change in the established or understood safety, effectiveness, and/or dosing requirements posed by the new combination. The following are examples of when additional preclinical or clinical safety information or new clinical studies may be appropriate for the drug/biologic constituent and/or the combination product:

1. Approved drug or biological product with a change in formulation, strength, route of administration, or delivery method;
2. New dosage (e.g., absolute dose, dosing duration, dosing regimen, or total exposure);

⁹ See consensus standards recognized by FDA

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>.

¹⁰ For purposes of this discussion, the term drug applies to drug and most biological product constituent parts.

¹¹ See *Guidance to Industry: Format and Content of Non-clinical Pharmacology/Toxicology Section of an Application* at <http://www.fda.gov/cder/guidance/index.htm>. General pharmacology-toxicology guidances may also be found at this location.

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3. New patient population, (e.g., pediatric, geriatric, pregnant or nursing women, or change in disease or disease status); or
4. Change in approved indication.

Regardless of the approval status of the drug/biologic constituent, the marketing application should contain appropriate data to establish the overall safety and effectiveness of the proposed new dosing regimen or indication as proposed in the combination product. For a combination product with a drug or biological product constituent that is already approved, it may be possible to tailor the pre-clinical development program to address safety questions posed by the new route or method of delivery, or the change in indication or population. The goal of these studies would be to evaluate changes that may result in a different extent or distribution of drug constituent exposure.¹² To the extent that the combination product permits local or systemic drug exposure that is greater than that occurring with approved dosing regimens, additional safety studies may also be needed to address the higher doses. New studies may be appropriate to evaluate the local/regional toxicity of a drug/device combination product administered directly to targeted tissue.

Other possible considerations when devising a development plan for a product incorporating a drug/biologic constituent include:

- *In vivo* pharmacokinetic (PK) studies may be necessary to assess changes in formulation, strength, route of administration, dosing, population or other factors that may alter the extent or time course of systemic exposure. These studies might be used to determine drug release kinetics such as release rate, local peak concentrations of the drug, local distribution and systemic bioavailability (C_{max} , T_{max} , etc.).
- Dose ranging or dose finding studies¹³ in humans may be appropriate to determine dose adjustments for safety/effectiveness when therapy is targeted to a local site.
- Acute and repeat dose toxicity studies using the new route of administration or method of delivery may be appropriate to determine the NOAEL (no observed adverse effect level) and toxicity profile of the combination product. Typically, these studies would evaluate the intended clinical formulation and dosing regimen/frequency that will closely approximate its use in clinical settings.
- Special safety studies may be appropriate for certain patient populations or risk profiles; e.g., hepatotoxicity, QT prolongation, special populations.
- Specific safety monitoring in the clinical study may be appropriate to obtain data on the novel aspects presented by the combination product; e.g., local toxicity for a new route of administration.¹⁴

¹² See *Guidance to Industry: Exposure-Response Relationships - Study Design, Data Analysis, and Regulatory Applications* at <http://www.fda.gov/cder/guidance/5341fnl.doc>.

¹³ See *ICH E4 Dose-Response Information to Support Drug Registration* at <http://www.fda.gov/cder/guidance/iche4.pdf>.

¹⁴ See *ICH E1A: The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* at <http://www.fda.gov/cder/guidance/iche1a.pdf>.

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In some instances, developers may be able to provide relevant information from the literature or may rely on prior agency findings to address these issues. When this is not possible, then additional studies may be necessary.

VI. ADDITIONAL PERSPECTIVES

A. Clinical Investigation

For most combination products, one investigational application (Investigational New Drug (IND) or Investigational Device Exemption (IDE) application) is submitted for the clinical investigation of the combination product as a whole. Generally, the regulatory guidance for INDs and IDEs provides substantial flexibility in considering how to address the issues posed by a particular product. Two such guidance documents that may be of interest to combination product developers are: (1) *Exploratory IND Studies*, which provides an alternative for exploring candidate products during research and development prior to selecting the composition for further development,¹⁵ and (2) guidance on changes that may occur during investigational development of a device.¹⁶

Clinical development questions frequently arise about trial design, sample size, statistical methods, clinical endpoints, appropriate number of clinical studies, and appropriate indications/claims. We recommend that you consider the science and technology of the combination product when determining sample size, use of statistical approaches, surrogate endpoints, techniques to measure drug levels in areas not typically accessible, or techniques to evaluate drug-device interactions. Although these issues are beyond the scope of this guidance, FDA encourages developers to seek early discussion with the Agency around these concerns.

For certain combination products that include a device constituent part, it may be necessary to evaluate the human factors of device use on the safety and effectiveness of the combination product. Such studies would evaluate how users operate the system in realistic, stressful conditions. In many cases, these studies include an assessment of all components and accessories necessary to operate and properly maintain the device; e.g., controls, displays, software, logic of operation, labels, instructions, analysis of critical tasks, use error hazard and risk analysis. We recommend that human factors evaluations take place early in the combination product development process to identify design features that may need modification before conducting the key studies to establish the safety and effectiveness of the combination product.

¹⁵ See *Guidance to Industry and Reviewers: Exploratory IND Studies* at <http://www.fda.gov/cder/guidance/7086fnl.pdf>.

¹⁶ See *Guidance to Industry: Changes or Modifications During the Conduct of a Clinical Investigation* at <http://www.fda.gov/cdrh/ode/guidance/1337.pdf>

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B. Manufacturing considerations

Manufacturing, scale-up, and quality management¹⁷ are important considerations during the development of a combination product. Manufacturing methodologies affect both premarket development and postmarket regulation. FDA encourages consideration of the manufacturing issues posed by the scientific and technical aspects of the drug, biological product, and device constituent parts, and of the combination product as a whole. FDA also encourages developers to carefully consider the effect of the manufacturing methods on the interaction of the constituent parts. For example, the stability of a combination product as a whole may be different than that of the separate constituent parts. Certain drug or biological product constituent parts may be altered or destroyed by terminal sterilization techniques. For constituent parts that use aseptic manufacturing techniques, developers are encouraged to implement manufacturing techniques to ensure aseptic control for the combination product.

During premarket investigation, once the preclinical and clinical studies begin, any potential change in the manufacturing process for the drug, biologic, or device constituents or for the combination product may affect the safety or effectiveness of the combination product as a whole. For example, changes in concentration, inactive ingredients, software, or in the methods to combine two constituent parts, could affect the performance characteristics of the combination product. When applying cellular constituent parts to a device, the performance characteristics may vary with the time and methods used for cellular incubation before application to the device constituent. Additionally, the applicable device constituent design controls would consider anticipated manufacturing changes during investigational development. In order to address such manufacturing considerations, it may be necessary to develop new manufacturing techniques, in-process testing, testing specifications, and other characterization methods to assess changes in the constituent parts and for the combination product as a whole. For certain developmental changes, additional bridging studies (in vitro, preclinical, or clinical) may be appropriate.

In addition to considering manufacturing changes that may occur during premarket development, FDA also recommends early consideration of anticipated postmarket manufacturing changes for the combination product or its constituent parts. FDA encourages manufacturers to establish arrangements with the manufacturers of constituent parts to maintain sufficient awareness of manufacturing changes in constituent parts that may occur during the premarket or postmarket period. Such awareness could help to ensure continued safety and effectiveness of the combination product by ensuring that the potential impact of a manufacturing change is evaluated in a manner appropriate for the stage of combination product development. As appropriate, these postmarket manufacturing changes may require careful review, validation and prior approval before marketing. For some products, it may be helpful to develop post-approval change protocols for further discussion with the Agency.

¹⁷ FDA's current thinking about good manufacturing practices for combination products is described in "Draft Guidance for Industry and FDA Staff: Current Good Manufacturing Practice for Combination Products," available at <http://www.fda.gov/oc/combination/OCLOvel1dft.html>. FDA intends to propose current good manufacturing practice regulations for combination products; see the April 24, 2006 Federal Register (71 FR 22565).

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C. Reliance on information not developed by the applicant

Investigational or marketing applications often contain trade secret or confidential commercial information. In some instances, developers may wish to provide all necessary information in one marketing application. However, for combination products being developed by more than one manufacturer, there may be a desire to provide necessary information to FDA while maintaining the confidentiality of each manufacturer's intellectual property. This can be accomplished by the application holder submitting to FDA a letter of authorized cross reference from the owner of the referenced material. This letter would grant FDA permission to consider the referenced material in its review of the current application. In general, the referenced information may be available from two sources:

1. Existing application: An existing investigational application (IND or IDE) or an existing marketing application (NDA, BLA, PMA or 510(k)) may provide information relevant to a new developer's application. In some instances, the application being cross referenced may be under co-review for use in the combination product. In other instances, the cross-referenced application may be approved for other purposes, but may have information relevant to the new use.
2. Master file: Master files provide an administrative method to submit confidential information to FDA when an appropriate investigational or marketing application for the constituent is not available. A master file is not a substitute for an investigational or marketing application. FDA neither approves nor disapproves master files; rather, information in a master file is considered in the context of a particular investigational or marketing application. It should be recognized that the information in a master file may be sufficient to support a marketing application for one product, while additional information may be necessary to support its use in another product. For example, this may occur when specific issues raised by the new use of a constituent are not addressed in the master file. Such information could be provided by supplementing the existing master file, or by providing the necessary information in the application under review. More information on drug master files may be found in 21 CFR 314.420 or at <http://www.fda.gov/cder/dmf/index.htm>. More information on device master files is available at http://www.fda.gov/cdrh/dsma/pmaman/appdxc.html#P7_2.

VII. EARLY INTERACTION AND COMMUNICATION WITH FDA

FDA strongly encourages early communication and discussion between developers, FDA review components and, as appropriate, OCP. Early dialogue allows developers to obtain initial feedback on the kinds of preclinical and clinical testing that may be necessary. Such communication may identify critical issues for product development and help to ensure an efficient development and approval process. Further, early and frequent communication provides the opportunity for FDA to establish its intercenter review team and to develop the

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appropriate scientific expertise to facilitate timely and efficient reviews of any future submissions.

CBER, CDER and CDRH provide guidance on milestone/collaboration meetings throughout the development process and submission of investigational and marketing applications. Pre-investigational (pre-IND and pre-IDE) meetings are particularly useful for discussing innovative combination products. Pre-marketing application meetings are also helpful to discuss application content, as well as the sequence and timing of modular applications or when more than one marketing application will be submitted for the combination product. Guidance on how to arrange developmental meetings can be obtained on the CDER,¹⁸ CBER¹⁹ and CDRH²⁰ websites.

The lead center should be contacted to schedule meetings in accordance with the procedures and milestones applicable to the lead center. We encourage developers to request participation from relevant review components from both the lead and consulting Centers, where appropriate. In addition, OCP is available formally or informally to address jurisdictional, developmental, premarket review, and postmarket concerns.

A. Where may I obtain additional information?

OCP is available as a resource to developers and review staff throughout the lifecycle (assignment, development, premarket review and postmarket regulation) of a combination product. The Office can be reached at (301) 427-1934 or by email at combination@fda.gov. In addition, the Office maintains an updated list of FDA guidance documents that developers may find helpful in the development of their products. The guidance is available at the Office's Internet Website at <http://www.fda.gov/oc/combo>.

In addition each center maintains a guidance webpage that provides comprehensive information on the types of constituents regulated in the center. The CDER Guidance webpage is accessible at <http://www.fda.gov/cder/guidance/index.htm>. The CDRH Guidance web page is accessible at <http://www.fda.gov/cdrh/guidance.html> and the device advice webpage is assessable at <http://www.fda.gov/cdrh/devadvice/>. The CBER Guidance web page is accessible at <http://www.fda.gov/cber/guidelines.htm>.

¹⁸ See <http://www.fda.gov/cder/guidance/3683fnl.pdf>.

¹⁹ See <http://www.fda.gov/cber/gdlns/ind052501.htm>.

²⁰ See <http://www.fda.gov/cdrh/devadvice/ide/print/approval.html> , and, *Early Collaboration Meetings Under the FDA Modernization Act, Final Guidance for Industry and CDRH Staff*; <http://www.fda.gov/cdrh/ode/guidance/310.html>



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 19 May 2011
2 EMA/CHMP/BWP/25360/2011
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Concept paper on the need for a guideline on process**
5 **validation of medicinal products containing biotechnology**
6 **derived proteins as active substance**
7

8 **DRAFT**
9

Agreed by Biologics Working Party	March 2011
Adoption by CHMP	19 May 2011
End of consultation (deadline for comments)	31 August 2011

10
11

Comments should be provided using this [template](#). The completed comments form should be sent to BWPSecretariat@ema.europa.eu

12

Keywords	<i>Process validation, biological active substance</i>

13



1. Introduction

This concept paper addresses the need to develop guidance on process validation of biotechnology derived active substances.

2. Problem statement

Guidelines related to the quality of Biotechnological/Biological products have been developed at the EU level, and several documents have been harmonised through the ICH process. However, these documents do not satisfactorily address the specific aspects of validation and evaluation for biotechnology derived products.

3. Discussion

Validation and evaluation are essential concepts when setting the manufacturing process steps of biotechnology derived products. The evaluation/validation data provide essential information on the reproducibility and robustness of the process steps and are an important element to guarantee consistency in the quality of the product. The data encompass studies that are performed on product and process steps representative of the commercial process and may cover a wide range of situations and experiments (e.g. full scale, pilot scale, laboratory scale, scaled-down), depending on the objectives of the evaluation/validation studies carried out during development (e.g. consistency, viral safety evaluation, process-related impurity clearance).

The currently approved guidelines address the control of Biotechnological/Biological products (i.e. ICH Q6B on specification and ICH Q5C on stability), and/or some specific issues or aspects of the process (i.e. ICH Q5A on viral safety, ICH Q5B on genetic stability, ICH Q5D on cell substrates and ICH Q5E on comparability). ICH Q11, currently under development, is aimed at addressing the description, development, control strategy and process evaluation/validation of active substances of biotechnological and chemical origins. Although ICH Q5 and ICH Q11 documents address several important aspects or concepts relating to the evaluation/validation for medicinal products containing biotechnology derived proteins as active substance, as illustrated above there is no guidance to cover other aspects such as process- and product-related impurity clearance (e.g. host cell proteins, DNA), column/membrane sanitization and life time, hold time, reprocessing, pooling of intermediates and selection of batches to be included in evaluation/validation studies. All these elements do contribute to a good understanding of the process and the resulting product, and are needed for the assessors at the time of evaluation of a marketing authorisation application.

It is well acknowledged that ICH Q8, Q9 and Q10 guidelines are progressively being implemented in the routine practice of manufacturers and marketing authorisation holders. However, whereas these guidelines provide a new approach on the management of quality and build up the quality at every step of the life cycle of a medicinal product, they do not provide practical recommendations on the necessary evaluation/validation studies to be filed on these specific aspects (new application or variations).

4. Recommendation

The Biologics Working Party (BWP) recommends developing a guideline on process evaluation/validation of medicinal products containing biotechnology derived proteins as active substance. This guideline should focus on data requirement for process validation/evaluation for submission of a marketing authorisation application or variation. This guideline will have to take into

55 account the existing guidances and new concepts and integrate them (by appropriate cross
56 referencing) in the evaluation/validation approach which will be described in the guideline.

57 **5. Proposed timetable**

58 It is anticipated that the draft guideline will be released for consultation in the first quarter of 2012,
59 followed by a 6 month external consultation period prior to finalisation of the document.

60 **6. Resource requirements for preparation**

61 BWP will be responsible for the drafting of this guideline. A drafting group should be formed, which will
62 meet at dedicated drafting group meetings and also in the margin of BWP meetings and via remote
63 conferencing. Where appropriate, a workshop between different stakeholders (assessors and inspectors
64 from national competent authorities, biotech companies...) may be required depending on the
65 comments that will be received following the external consultation.

66 **7. Impact assessment (anticipated)**

67 The guidance will clarify requirements for regulators and industry with respect to process
68 evaluation/validation of medicinal products containing biotechnology derived proteins as active
69 substance.

70 **8. Interested parties**

71 Competent authorities of the Member States and pharmaceutical industry

72 **9. References to literature, guidelines, etc.**

73 ICH Q5A (CPMP/ICH/295/95), Q5B (CPMP/ICH/139/95), Q5C (CPMP/ICH/138/95), Q5D
74 (CPMP/ICH/294/95) and Q5E (CPMP/ICH/5721/03) guidelines

75 ICH Q6B (CPMP/ICH/365/96) guideline

76 ICH Q7 (CPMP/ICH/4106/00) guideline

77 Draft ICH Q11 guideline

78 CPMP Position Statement on DNA and host cell proteins (HCP) impurities, routine testing versus
79 validation studies (CPMP/BWP/382/97)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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ICH guideline Q8, Q9 and Q10 - questions and answers volume 4

Step 5

Transmission to CHMP for information	December 2010
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ICH guideline Q8, Q9 and Q10 - questions and answers volume 4

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1. Introduction

This Questions and Answers document (Q&A) refers to the current working procedure of the ICH Q-IWG on implementing the guidelines of Q8, Q9 and Q10 which have been approved by the ICH Steering Committee.

The benefits of harmonizing technical requirements across the ICH regions can only be reached if the various Q-ICH guidelines are implemented and interpreted in a consistent way across the three regions. Implementation Working Group is tasked to develop Q&As to facilitate implementation of existing guidelines.

References

ICH Q8(R2)	Pharmaceutical Development	approved Aug. 2009
	<i>Part I: 'Pharmaceutical Development'</i>	<i>approved Nov. 10 2005</i>
	<i>Part II: 'Annex to Pharmaceutical Development'</i>	<i>approved Nov. 13 2008</i>
	http://www.ich.org/LOB/media/MEDIA4986.pdf	
ICH Q9	Quality Risk Management	approved Nov. 09 2005
	http://www.ich.org/LOB/media/MEDIA1957.pdf	
ICH Q10	Pharmaceutical Quality Systems	approved Jun. 04 2008
	http://www.ich.org/LOB/media/MEDIA3917.pdf	

Q8, Q9 and Q10 - questions and answers volume 4

1 1.1. For general clarification

Date of Approval		Question	Answer
1	June 2009	Is the minimal approach accepted by regulators?	Yes. The minimal approach as defined in Q8(R2) (sometime also called 'baseline' or 'traditional' approach) is the expectation which is to be achieved for a fully acceptable submission. However the 'enhanced' approach as described in ICH Q8(R2) is encouraged (Ref. Q8(R2) Appendix 1).
2	Oct. 2009	What is an appropriate approach for process validation using ICH Q8, Q9 and Q10?	The objective of process validation are unchanged when using ICH Q8, Q9 and Q10. The main objective of process validation remains that a process design yields a product meeting its pre-defined quality criteria. ICH Q8, Q9 and Q10 provide a structured way to define product critical quality attributes, design space, the manufacturing process and the control strategy. This information can be used to identify the type and focus of studies to be performed prior to and on initial commercial production batches. As an alternative to the traditional process validation, continuous process verification [see definition in ICH Q8R(2) glossary] can be utilised in process validation protocols for the initial commercial production and for manufacturing process changes for the continual improvement throughout the remainder of the product lifecycle.
3	Oct. 2009	How can information from risk management and continuous process verification provide for a robust continual improvement approach under ICH Q8, Q9 and Q10?	Like the product itself, process validation also has a lifecycle (process design, process qualification and ongoing process verification). A risk assessment conducted prior to initial commercial validation batches can highlight the areas where particular focus and data is needed to demonstrate the desired high level of assurance of commercial process robustness. Continual monitoring (e.g. via Continuous Process Verification)

Date of Approval	Question	Answer
		can further demonstrate the actual level of assurance of process consistency and provide the basis for continual improvement of the product. Quality Risk Management methodologies of ICH Q9 can be applied throughout the product lifecycle to maintain a state of process control.

2. Quality by design topics

Date of Approval	Question	Answer
1 April 2009	Is it always necessary to have a Design Space (DS) or Real Time Release (RTR) testing to implement QbD?	Under Quality by Design, establishing a design space or using real time release testing is not necessarily expected [ICH Q8(R2), Step 4].

2.1. Design space

Date of Approval	Question	Answer
1 April 2009	Is it necessary to study multivariate interactions of all parameters to develop a design space?	No, the applicant will need to justify the choice of material attributes and parameters for multivariate experimentation based on risk assessment and desired operational flexibility.
2 April 2009	Can a design space be applicable to scale-up?	Yes, when appropriately justified [additional details see Q8(R2) Section 2.4.4]. An example of a scale-independent design space is provided in the EFPIA Mock P2 document [EFPIA Mock P2 submission on "Explain": Chris Potter, Rafael Beerbohm, Alastair Coupe, Fritz Erni, Gerd Fischer, Staffan Folestad, Gordon Muirhead, Stephan Roenninger, Alistair Swanson, A guide to EFPIA's "Mock P.2" Document, Pharm. Tech. (Europe), 18, December 2006, 39-44]. This example may not reflect the full regulatory requirements for a scale-

Date of Approval	Question	Answer
3	April 2009 Can a design space be applicable to a site change?	up. Yes, it is possible to justify a site change using a site independent design space based on a demonstrated understanding of the robustness of the process and an in depth consideration of site specific factors, e.g., equipment, personnel, utilities, manufacturing environment, and equipment. There are region specific regulatory requirements associated with site changes that need to be followed.
4	April 2009 Can a design space be developed for single and/or multiple unit operations?	Yes, it is possible to develop a design space for single unit operations or across a series of unit operations [see Q8(R2) Section 2.4.3].
5	April 2009 Is it possible to develop a design space for existing products?	Yes, it is possible. Manufacturing data and process knowledge can be used to support a design space for existing products. Relevant information should be utilised from e.g., commercial scale manufacturing, process improvement, CAPA and development data. For manufacturing operations run under narrow operational ranges in fixed equipment, an expanded region of operation and an understanding of multi-parameter interactions may not be achievable from existing manufacturing data alone and additional studies may be needed to develop a design space. Sufficient knowledge should be demonstrated and the design space should be supported experimentally to investigate interactions and establish parameter/attribute ranges.
6	April 2009 Is there a regulatory expectation to develop a design space for an existing product?	No, development of design space for existing products is not necessary unless the applicant has a specific need and desires to use a design space as a means to achieve a higher degree of product and process understanding. This may increase manufacturing flexibility and/or robustness.
7	June 2009 Can a design space be applicable to formulation?	Yes, it may be possible to develop formulation (not component but rather composition) design space consisting of the ranges of excipient amount and its physicochemical properties (e.g., particle size distribution, substitution degree of polymer) based on an enhanced knowledge over a wider range of

Date of Approval	Question	Answer
		material attributes. The applicant should justify the rationale for establishing the design space with respect to quality attributes such as bioequivalence, stability, manufacturing robustness etc. Formulation adjustment within the design space depending on material attributes does not need a submission in a regulatory post approval change.
8 June 2009	Does a set of proven acceptable ranges alone constitute a design space?	No, a combination of proven acceptable ranges (PARs) developed from univariate experimentation does not constitute a design space [see Q8(R2), Section 2.4.5.]. Proven acceptable ranges from only univariate experimentation may lack an understanding of interactions between the process parameters and/or material attributes. However proven acceptable ranges continue to be acceptable from the regulatory perspective but are not considered a design space [see ICH Q8(R2) Section 2.4.5]. The applicant may elect to use proven acceptable ranges or design space for different aspects of the manufacturing process.
9 Nov 2010	Should the outer limits of the Design Space be evaluated during process validation studies at the commercial scale?	No. There is no need to run the qualification batches at the outer limits of the design space during process validation studies at commercial scale. The design space must be sufficiently explored earlier during development studies (for scale up see also chapter 2.1 Design Space Q02; for life cycle approach see chapter 1.1 for general clarification Q03).

4 2.2. Real time release testing

Date of Approval	Question	Answer
1 April 2009	How is batch release affected by employing real time release testing?	Batch release is the final decision to release the product to the market regardless whether RTR testing or end product testing is employed. End product testing involves performance of specific analytical procedures on a defined sample size of the final product after completion of all processing

Date of Approval	Question	Answer
		for a given batch of that product. Results of real time release testing are handled in the same manner as end product testing results in the batch release decision. Batch release involves an independent review of batch conformance to predefined criteria through review of testing results and manufacturing records together with appropriate GMP compliance and quality system, regardless of which approach is used.
2	April 2009 Does real time release testing mean elimination of end product testing?	Real time release testing does not necessarily eliminate all end product testing. For example, an applicant may propose RTR testing for some attributes only or not all. If all CQAs (relevant for real time release testing) are assured by in-process monitoring of parameters and/or testing of materials, then end product testing might not be needed for batch release. Some product testing will be expected for certain regulatory processes such as stability studies or regional requirements.
3	April 2009 Is a product specification still necessary in the case of RTR testing?	Yes, product specifications [see ICH Q6A and Q6B] still need to be established and met, when tested.
4	April 2009 When using RTR testing, is there a need for stability test methods?	Even where RTR testing is applied, a stability monitoring protocol that uses stability indicating methods is required for all products regardless of the means of release testing. [see ICH Q1A and ICH Q5C].
5	April 2009 What is the relationship between Control Strategy and RTR testing?	RTR testing, if utilized, is an element of the Control Strategy in which tests and/or monitoring can be performed as in process testing (in-line, on-line, at-line) rather than tested on the end product.
6	April 2009 Do traditional sampling approaches apply to RTR testing?	No, traditionally sampling plans for in-process and end-product testing involve a discrete sample size that represents the minimal sampling expectations. Generally, the use of RTR testing will include more extensive on-line/in-line measurement. A scientifically sound sampling approach should be developed, justified, and implemented.
7	April 2009 If RTR testing results fail or trending toward failure, can end-product testing be used to release the batch?	No, in principle the RTR testing results should be routinely used for the batch release decisions and not be substituted by end-product testing. Any failure should be investigated and trending should be followed up

Date of Approval	Question	Answer
		appropriately. However, batch release decisions will need to be made based on the results of the investigations. The batch release decision needs to comply with the content of the marketing authorisation and GMP compliance.
8 June 2009	What is the relationship between in-process testing and RTR testing?	In-process testing includes any testing that occurs during the manufacturing process of drug substance and/or finished product. Real time release testing includes those in-process tests that directly impact the decision for batch release through evaluation of Critical Quality Attributes.
9 June 2009	What is the difference between 'real time release' and 'real time release testing'?	The definition of 'real time release testing' in Q8(R2) is 'the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data, which typically includes a valid combination of measured material attributes and process controls. The term 'Real time release' in the Q8(R2), <i>Step 2</i> document was revised to 'Real time release testing' in the final Q8(R2) Part II document to fit the definition more accurately and thus avoid confusion with batch release.
10 June 2009	Can surrogate measurement be used for RTR testing?	Yes, RTR testing can be based on measurement of a surrogate (e.g., process parameter, material attribute) that has been demonstrated to correlate with an in process or end product specification [see ICH Q8(R2); Section 2.5.].
11 Oct. 2009	What is the relationship between RTR testing and Parametric Release?	Parametric release is one type of RTR testing. Parametric release is based on process data (e.g. temperature, pressure, time for terminal sterilization, physicochemical indicator) rather than the testing of material and/or a sample for a specific attribute.

5

6

2.3. Control strategy

Refer to the definition of control strategy provided in the ICH Q10 glossary: Q10 Control Strategy definition: 'a planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.'

Date of Approval	Question	Answer
1 April 2009	What is the difference in a control strategy for products developed using the minimal approach vs. 'quality-by-design' approach?	Control strategies are expected irrespective of the development approach. Control strategy includes different types of control proposed by the applicant to assure product quality (Section 3.2.1 ICH Q10), such as in-process testing and end-product testing. For products developed following the minimal approach, the control strategy is usually derived empirically and typically relies more on discrete sampling and end product testing. Under QbD, the control strategy is derived using a systematic science and risk-based approach. Testing, monitoring or controlling is often shifted earlier into the process and conducted in-line, on-line or at-line testing.
2 April 2009	Are GMP requirements different for batch release under QbD?	No, the same GMP requirements apply for batch release under minimal and QbD approaches.
3 April 2009	What is the relationship between a Design Space and a Control Strategy?	A control strategy is required for all products. If a Design Space is developed and approved, the Control Strategy [see ICH Q8(R2), Part II, Section 4] provides the mechanism to ensure that the manufacturing process is maintained within the boundaries described by the Design Space.
4 June 2009	What approaches can be taken in the event of on-line/in-line/at-line testing or monitoring equipment breakdown?	The control strategy provided in the application should include a proposal for use of alternative testing or monitoring approaches in cases of equipment failure. The alternative approach could involve use of end product testing or other options, while maintaining an acceptable level of quality. Testing or monitoring equipment breakdown needs to be managed in the context of a deviation under the Quality System and can be covered

Date of Approval	Question	Answer
5 Oct. 2009	Are product specifications different for minimal versus QbD approaches?	by GMP inspection. In principle no, the same product specifications are needed for minimal and QbD approaches. For a QbD approach, the control strategy may allow achieving the end product specifications via real time release testing approaches [see ICH Q8(R2), Appendix 1]. Product must meet specification, when tested.

3. Pharmaceutical quality system

Date of Approval	Question	Answer
1 April 2009	What are the benefits of implementing a Pharmaceutical Quality System (in accordance with ICH Q10)?	The benefits are: - Facilitated robustness of the manufacturing process, through facilitation of continual improvement through science and risk-based post approval change processes; - Consistency in the global pharmaceutical environment across regions; - Enable transparency of systems, processes, organisational and management responsibility; - Clearer understanding of the application of a Quality System throughout product lifecycle; - Further reducing risk of product failure and incidence of complaints and recalls thereby providing greater assurance of pharmaceutical product consistency and availability (supply) to the patient; - Better process performance; - Opportunity to increase understanding between industry and regulators and more optimal use of industry and regulatory resources. Enhance manufacturer's and regulators' confidence in product quality; - Increased compliance with GMPs, which builds confidence in the regulators and may result in shorter inspections.

Date of Approval	Question	Answer
2 April 2009	How does a company demonstrate implementation of PQS in accordance with ICH Q10?	When implemented, a company will demonstrate the use of an effective PQS through its documentation (e.g., policies, standards), its processes, its training/qualification its management its continual improvement efforts, and its performance against pre-defined Key Performance Indicators [see ICH Q10 glossary on 'Performance indicator']. A mechanism should be established to demonstrate at a site how the PQS operates across the product lifecycle, in an easily understandable way for management, staff and regulatory inspectors, e.g., a quality manual, documentation, flowcharts, procedures. Companies can implement a program in which the PQS is routinely audited in-house (i.e., internal audit program) to ensure that the system is functioning at a high level.
3 April 2009	Is it necessary to describe the PQS in a regulatory submission?	No, however relevant elements of the PQS, such as quality monitoring system, change control and deviation management may be referenced as part of the control strategy as supporting information.
4 April 2009	Will there be certification that the PQS is in accordance with ICH Q10?	No. There will not be a specific ICH Q10 certification programme.
5 April 2009	How should the implementation of the design space be evaluated during inspection of the manufacturing site?	Inspection should verify/assess that manufacturing operations are appropriately carried out within the Design Space. The inspector in collaboration with the assessor, where appropriate, should also verify successful manufacturing operations under the Design Space and that movement within the Design Space is managed within the company's change management system [see ICH Q10, Section 3.2. Table III].
6 April 2009	What should be done if manufacturing operations run inadvertently outside of the Design Space?	This should be handled as a deviation under GMP. For example unplanned 'one-off' excursions occurring as a result of unexpected events, such as operator error or equipment failure, would be investigated, documented and dealt with as a deviation in the usual way. The results of the investigation may contribute to the process knowledge, preventive actions and continual improvement of the product.
7 June	What information and documentation of the development	Pharmaceutical development information (e.g., supporting information on

Date of Approval	Question	Answer
2009	studies should be available at a manufacturing site?	design space, chemometric model, risk management,...) is available at the development site. Pharmaceutical development information which is useful to ensure the understanding of the basis for the manufacturing process and control strategy, including the rationale for selection of critical process parameters and critical quality attributes should be available at the manufacturing site. Scientific collaboration and knowledge sharing between pharmaceutical development and manufacturing is essential to ensure the successful transfer to production.
8 June 2009	Can process parameters be adjusted throughout the product lifecycle?	Process parameters are studied and selected during pharmaceutical development and monitored during commercial manufacturing. Knowledge gained could be utilized for adjustment of the parameters as part of continual improvement of the process throughout the lifecycle of the drug product (see ICH Q10, Section 3.).

4. ICH new quality guidelines' impact on GMP inspection practices

Date of Approval	Question	Answer
1 April 2009	How will <u>product-related</u> inspections differ in an ICH Q8, Q9 and Q10 environment?	In the case of product-related inspection (in particular pre-authorisation) depending on the complexity of the product and/or process, there could be a need for greater collaboration between inspectors and assessors for example for the assessment of development data. The inspection would normally occur at the proposed commercial manufacturing site and there is likely to be greater focus on enhanced process understanding and understanding relationships e.g., Critical Quality Attribute (CQAs), Critical Process Parameters (CPPs). It will also extend into the application and implementation of quality risk management principles, as supported by the Pharmaceutical Quality System (PQS).

Date of Approval	Question	Answer
2 April 2009	How will <u>system-related</u> inspections differ in an ICH Q8, Q9 and Q10 environment?	The inspection process will remain similar. However upon the implementation of ICH Q8, Q9 and Q10, inspections will have greater focus (but not only) on how the PQS facilitates the use of e.g., Quality Risk Management methods, implementation of design space and change management [see ICH Q10].
3 Oct. 2009	How is control strategy approved in the application and evaluated during inspection?	Elements of control strategy submitted in the application will be reviewed and approved by the regulatory agency. However, additional elements are subject to inspection (as described in Q10).

5. Knowledge management

Date of Approval	Question	Answer
1 April 2009	How has the implementation of ICH Q8, Q9, and Q10 changed the significance and use of knowledge management?	Q10 defines knowledge management as: 'Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components'. Knowledge management is not a system; it enables the implementation of the concepts described in ICH Q8, Q9 and Q10. Knowledge Management is not a new concept. It is always important regardless of the development approach. Q10 highlights knowledge management because it is expected that more complex information generated by appropriate approaches (e.g., QbD, PAT, real-time data generation and control monitoring systems) will need to be better captured, managed and shared during product life-cycle. In conjunction with Quality Risk Management, Knowledge Management can facilitate the use of concepts such as prior knowledge (including from other similar products), development of design space, control strategy, technology transfer, and continual improvement across the product life cycle.

Date of Approval	Question	Answer
2	April 2009 Does Q10 suggest an ideal way to manage knowledge?	No. Q10 provides a framework and does not prescribe how to implement knowledge management. Each company decides how to manage knowledge, including the depth and extent of information assessment based on their specific needs.
3	April 2009 What are potential sources of information for Knowledge Management?	Some examples of knowledge sources are: Prior knowledge based on experience obtained from similar processes (internal knowledge, industry scientific and technical publications) and published information (external knowledge: literature and peer-reviewed publications); Pharmaceutical development studies; Mechanism of action; Structure/function relationships; Technology transfer activities; Process validation studies; Manufacturing experience e.g. - Internal and Vendor audits; - Raw material testing data; Innovation; Continual improvement; Change management activities; Stability reports; Product Quality Reviews/Annual Product Reviews; Complaint Reports; Adverse event reports (Patient safety); Deviation Reports, Recall Information; Technical investigations and/or CAPA reports; Suppliers and Contractors; Product history and /or manufacturing history; Ongoing manufacturing processes information (e.g., trends).

Date of Approval	Question	Answer
		Information from the above can be sourced and shared across a site or company, between companies and suppliers/contractors, products and across different disciplines (e.g., development, manufacturing, engineering, quality units).
4	April 2009 Is a specific dedicated computerised information management system required for the implementation of knowledge management with respect to ICH Q8, Q9 and Q10?	No, but such computerised information management systems can be invaluable in capturing, managing, assessing and sharing complex data and information.
5	June 2009 Will regulatory agencies expect to see a formal knowledge management approach during inspections?	No. There is no added regulatory requirement for a formal knowledge management system. However it is expected that knowledge from different processes and systems will be appropriately utilised. Note: 'formal' means: it is a structured approach using a recognised methodology or (IT-) tool, executing and documenting something in a transparent and detailed manner.

6. Software solutions

Date of Approval	Question	Answer
1	April 2009 With the rapid growth of the new science and risk-based quality paradigm coupled with the IWG efforts to facilitate globally consistent implementation of Q8, Q9, and Q10, a number of commercial vendors are now offering products that are being marketed as 'ICH compliant solutions' or ICH Q8, 9 & 10 Implementation software, etc. Is it necessary for a pharmaceutical firm to purchase these products to achieve a successful implementation of these ICH	No. The ICH Implementation Working Group has not endorsed any commercial products and does not intend to do so. ICH is not a regulatory agency with reviewing authority and thus does not have a role in determining or defining 'ICH compliance' for any commercial products. While there will likely be a continuous proliferation of new products targeting the implementation of these ICH guidelines, firms will need to carry out their own evaluation of these products relative to their business needs.

Date of Approval	Question	Answer
	guidelines within their companies?	

GMPs for APIs:

“How to do” Document

Interpretation of the ICH Q7a Guide

Version 6

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Chapter 1 Introduction

1.1 Objective

Historical Background

When the initiative was taken by PIC/S at the Canberra meeting in September 1996 to draft a globally harmonised Good Manufacturing Practices (GMP) guide for the Production of Active Pharmaceutical Ingredients (API's), the recommendation was made that this should essentially be a "what to do", rather than a "how to do" document.

After that initiative the International Conference on Harmonisation (ICH), which consists of the three major pharmaceutical regions of the world - USA, Japan and Europe - took the topic on board. The ICH established an Expert Working Group (EWG) which membership was due to the importance of the topic extended beyond the three regions to WHO, PIC/S members, India, China and OTC and Generic industry representatives. The EWG, of which CEFIC APIC was a member of, has compiled the 'GMPs for APIs' Guide within 2 ½ years time. The document was finalised by November 2000 and is now at the stage to be implemented within the three regions.

Purpose of the Document

This document was written by experts from the European Industry (CEFIC APIC). It is essentially an interpretation of "how to" implement the ICH Q7a Guide based on practical experience. Other relevant publications (e.g. ISPE Baseline Guides, other ICH Guidelines) were taken into account and references included.

This document does not intend to provide an exhaustive list of "how to" comply with the above mentioned requirements and recommendations. It does however provide examples of commonly applied solutions and practical assistance on how requirements and recommendations can be met and /or interpreted.

Industry should avoid needless paperwork and administrative burden. As indicated in the Q7a document the focus should be - for the benefit of the patient - on identifying the critical controls and procedures that assure the quality of the API. Therefore, sound scientific judgement should prevail when setting up a quality system incorporating GMP.

Finally, APIC/CEFIC cannot guarantee that adhering to the principles laid down in this document will consistently result in trouble free inspections. Adoption of the guidance given will however provide both industry and regulators with a much greater confidence in the quality of global bulk active pharmaceutical ingredients manufacture.

The word « should » is extensively used in the final version of the ICH Q7a Guide. It indicates requirements and recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative that can be shown to provide at least an equivalent level of quality assurance. Hence, « should » does not mean that because it is only a «should», and not a «must», then this requirement does not have to be met.

This document is meant to be a "living document" to describe current practice and

	to help with the implementation of the GMP Guide for APIs. Suggestions and/or questions from industry or regulators to CEFIC APIC (http://apic.cefic.org) are welcomed. These will be discussed regularly by the industry experts and clarifications and improvements incorporated into the document. Regulatory Requirements Companies should be aware that the regulatory filing requirements might differ from the application of GMP as defined by Q7a. There may be cases where more information may be required by regulatory authorities, but inspections for compliance with the Q7a Guide should only cover the GMP relevant steps.

1.2 Regulatory Applicability

	-

1.3 Scope

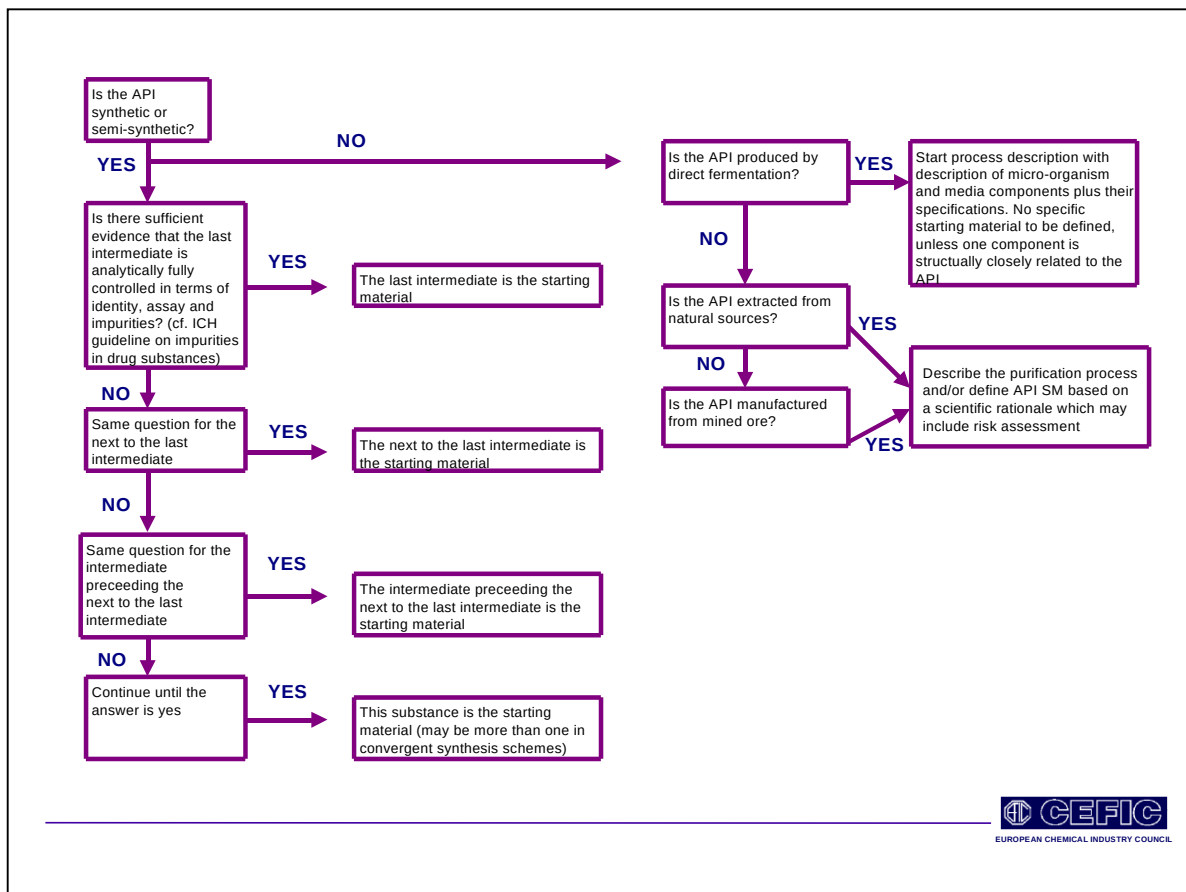
	API Starting Materials Companies are responsible for proposing the API Starting Material(s). This is one of the most significant changes proposed in the ICH Q7a document. The technical and quality groups should work closely with regulatory groups to ensure no disagreement occurs on the proposed starting materials. Ideally the registration of New API's will start from the same Starting Materials defined from a GMP perspective. However, based on current regulatory requirements it is likely that the regulatory authorities will require further information on API Starting Materials where only one or two synthetic steps exist between the API starting Material and the API or where the API Starting Material is an API itself. The companies should review the synthetic process of each API and based on technical and quality assessments define what are the significant structural fragments beyond which the GMP standards defined in ICH Q7a should apply. In general, the source of the API Starting Materials is not the major factor. The regulatory authorities may also require further details for late stage API Starting Materials, though recent examples are known that in specific cases FDA has accepted final intermediates as API Starting Materials (e.g. the widely commercially available substance 6-APA for the manufacture of semi-synthetic penicillin's)

Guidance on How To Define API Starting Materials

- Follow the guidance given in ICH Q7A and involve technical, quality and regulatory departments in agreeing the definition of the API Starting Materials. Where possible use the same definition of API starting material in regulatory filings and in defining the steps for which the GMP requirements of ICH Q7a apply.
- Further guidance on How To Define the API Starting Materials and regulatory strategy is given in the article:
 - “The Active Pharmaceutical Ingredients Starting Material (APISM) and other materials in API manufacture: Scientifically-based principles for the Common Technical Dossier” by Helga Möller and Chris Oldenhof, Drug Information Journal, Volume 33, Number 3, 1999, pages 755 – 761.
 - See also Eudralex Vol. 2b, page 162 (“Validation of the process should be carried out...for steps of the manufacturing process which are critical for the product”)
- The API Starting Material Decision Tree, developed by CEFIC/APIC and FIP, is the central feature of this guidance (see table at the end of the chapter).
- Where the proposed API Starting Material is close to the API itself ensure that details on the synthetic process and analytical controls used to manufacture the API Starting Material are available in case these would still be (justifiably) requested by the regulators. Where the API Starting Material is a commercial molecule the requirement to provide these details (if needed for confidentiality reasons: directly to the authorities only) may be included in the commercial contract.
- Similarly, Change Control requirements should be defined in the commercial contract for supply of API Starting Materials. Any significant changes to the synthetic route, analytical controls or specifications by the manufacturer of the API Starting Materials in general needs notification to and acceptance by the API manufacturer.
- While API Starting Materials do not require to be manufactured to the GMP requirements defined in ICH Q7a, manufacturers of intermediates and / or API's should have a system for evaluating the suppliers of critical materials (Reference Q7a Section 7.11). Appropriate qualification of API Starting Material suppliers is required.
- Companies should consider redefining the API Starting Material for well-established products. This offers the opportunity to reduce the overall GMP requirements for early manufacturing steps and to shift the focus to be on the control of the critical synthetic steps starting from the redefined API Starting Materials. Any proposed re-definitions to API Starting Materials should of

course be agreed with the regulatory authorities. The FDA have already indicated their willingness to reduce the filing requirements for certain well established "Qualified Products", including those relating to the final API synthesis steps.

Table: Decision Tree for help to define the API Starting Material



Chapter 2 Quality management

2.1 Principles

Among GMP other aspects, such as quality systems, environmental controls, and safety, are necessary to be taken into account in order to be in compliance with regulations. Business efficiency and continuous improvement are needed to be competitive. Therefore GMP compliance should be incorporated into an overall Quality Management Systems (QMS) as it is recommended in the EU GMP philosophy.

The importance of an effective QMS on customer relations, continuous improvement, regulatory compliance and inspection readiness should be pointed out, which directly ensures benefit to the patient.

To implement a QMS integrating GMP issues, please refer to the Guide "Quality Management System for Active Pharmaceutical Ingredients Manufacturers", APIC, September 2005.

2.10	Company management should empower Quality responsibility to the appropriate organisational functions to apply the Quality policy and procedures. Assignment of clear Roles & Responsibilities for duties and decisions is the basic rule and can be achieved by e.g. process descriptions including principles of RASCI (Responsible, Accountable, Consulted, Supportive and Informed) and decision trees. Delegated responsibilities should be trained, documented and periodically re-trained.
2.11	A clearly defined QMS (as defined e.g. in the APIC Guide (see above), ICH Q10 and ISO 9001: 2000 or later) integrating API GMP requirements, should be documented, implemented and described e.g. in the Quality Policy.
2.12	-
2.13	For the release of APIs there is no need for a "Qualified Person" (pharmacist) as defined by the European GMP Guideline (EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4: EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use) unless required by a specific law of the EU member state. The responsibilities for quality duties (e.g. process and control review, validation, change control, equipment qualification, batch documentation review, batch release, regulatory compliance, auditing, deviation handling, OOS treatments and complaint investigation) should be clearly assigned to one or more person(s) or function(s). The QU should be involved in many, if not all, of these issues. If the QA and QC department are separated units the roles and responsibilities of each unit must be clearly described and approved by the management.
2.14	Release of raw materials and intermediates meeting the specifications (for internal use only) by Production is acceptable, provided QU has approved specifications and test methods. Production personnel should be adequately trained for these duties, the training recorded and all equipment used qualified and calibrated at regular intervals. The QU, as part of their responsibility for batch release, has the right to review all test results and data. APIs and intermediates (for use outside of the control of the company) have to be released by a designated person of the QU. Deputy(s) for such designated person should be nominated.
2.15	All activities should be directly recorded at the time they are performed in legible

	documents like note-books, electronic records, etc., which are retrievable and traceable. Recording in non-traceable documents like a blank sheet of paper (re-writing afterwards into traceable documents) is not acceptable. Electronic documents and recording requires appropriate validation of the systems used (see chapter 5.4 and 6.10).
2.16	Documented explanations should be in place for every deviation. When deviations are considered critical, the QU should make sure that a formal investigation occurs, the findings should be recorded and, if defined, corrective actions should be implemented. See chapter 8.15 for a more detailed explanation.
2.17	The release of an API or intermediate does not automatically require that all corrective measures or actions identified in deviation investigations have to be completed in advance (e.g. corrective actions related to ongoing training, maintenance, process investigations).
2.18	As an example a regular report system should be made available to senior management by the QU informing of acute occurrences (quality related complaints, critical deviations, recalls, etc.). Senior management should review and agree any recommendations and ensure that appropriate resources are made available. Quality (or: key) performance indicators <u>could</u> be installed to evaluate continuous quality improvement of the department.

2.2 Responsibilities of the Quality Unit(s)

2.20	QU duties may be delegated to other departments/functions provided there are systems in place to ensure that the QU has adequate control / supervision. Different levels of control depending on the nature of the activity are required by ICH: "make sure" (for example: put systems in place, verify by auditing, assigns responsibilities), "be involved" (means personal involvement of the QU responsible) or "establishing" (QU issues a system or procedure on its assigned duties).
2.21	-
2.22	Although in this section it is stated "...should not be delegated" it is likely that company's will face problems during inspections if they come up with alternatives; this "should" has to be interpreted as "must". Only the batch production records of critical (Reference to critical see Glossary) steps (a step could be the entire unit operation, e.g. conversion of the final intermediate to the API or a single parameter such as temperature control at an earlier step) including laboratory records have to be reviewed by the QU, whilst the review of all other steps may be delegated (6.71). (sub-point 3). There should be a system in place defining what changes are likely to "impact intermediate or API quality" (sub-point 9). Nevertheless any change has to be evaluated and communicated. Stability data for intermediates are only required if they are intended to be sold (for reference see chapter 11.60), but there isn't the need to apply a full stability program as described in ICH Q1a and Q1b documents. In many instances, a retest of the material prior to use or shipment is sufficient to demonstrate that the product is still meeting its specifications. (However it is recommended to derive some data during the develop-

	ment phase or during validation to support storage periods of intermediates during campaign production or storage of left-over between two campaigns.) For details see also chapter 8.2.1. (sub-point 14) For filed specifications of Raw Materials and Intermediates, documented periodical review by the quality unit for delegated release to production should occur (ref. 2.5).

2.3 Responsibility for Production Activities

2.30	An additional advice for the assignment of quality related duties to Production and other functions / departments can be found in "EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4: EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use."

2.4 Internal Audits (Self-Inspections)

2.40	• See draft of CEFIC 'Auditing' Guideline for how to manage an effective internal audit/self inspection programme. Internal Audits (Self Inspections) are a valuable management tool to evaluate if the company is in compliance with the principles of GMP and additional requirements of the company which are integrated in the QMS. The evaluation should be made by trained auditors, experienced in auditing skills and recruited from various departments of the company, if possible. Quality Inspection Teams (QIT) of normally 2 persons are recommended, however (depending on the focus of the audit) recruiting of additional experts (e.g. engineers, micro-biologists etc.) could increase audit efficiency. QU should always be represented in a team, but not always taking the lead for not being accused to be the "policeman". The QU should be responsible for co-ordinating activities such as follows: • pre-audit meetings for the QIT (brain storming) • identifying major areas of concern and preparation of questions (questionnaire) • collecting historic information such as deviations, changes, complaints, previous internal audit reports • issuing the agenda and distribution to the auditee in due time • co-ordinating the activities of the QIT • starting the (internal) audit and summarising the findings in a close out meeting • issuing the audit report, on the basis of the close out meeting • propose corrective measures or improvements to management • schedule (propose) a re-audit in case of major findings • follow-up. Other members of the QIT could be involved in asking and taking extensive notes. The whole auditing process should be clearly defined and the following standard documents should be considered to be available in a generic layout form: • Definition of auditing process, system or product • Covering Letter • Report Form • Audit Team Evaluation Form • Follow-up Report • Training Programme

	The frequency of the self-inspections should be based on risk (a formal risk assessment may not be necessary) as well as the compliance status of the area to be audited. It may vary from half a year to three years, and the rationale behind the frequency should be documented. The compliance status of the area to be audited and may vary from half a year to three years. All participants in the QIT should have the commitment from the management to use the specified time for preparing, performing and reporting the internal audit. Also un-announced audits or spot checks should be considered besides the “normal” audit programme. If possible internal audits should not take more than to 3 - 4 hours. Remember to include at a minimum twice the time for preparing and writing the audit reports. It is important to define deadlines for issuing (recommendation: 2 weeks) and finalising (recommendation: 4 weeks) the report and for the first follow-up meeting. The internal Audit Report as well as the Follow-up Report should be kept confidential and should not be shown to external personnel, especially inspectors from authorities. All (Internal) Audit Reports should be made available for the management, and the findings discussed. Management is responsible to initiate necessary corrective actions and investments. If the API manufacturer at the same time the MA holder for the final drug product, there is an expectation that the finished product QP has access to all internal audit reports.
2.41	-

2.5 Product Quality Review

2.50	The major objective of the Product Quality Review is to evaluate the compliance status of the manufacture (process, packaging, labelling and tests) and to identify areas of improvement based on the evaluation of key data. Product quality reviews should not be solely performed by QU personnel. It is important that other departments, like Production, Engineering, Maintenance, Purchase, etc. are also involved. QU is held responsible for the release and approval of the final report. To ensure that key data is reviewed it is essential for each production process to identify the critical in process controls and critical API (or relevant intermediate) test results. These would normally be the critical API test results which may be used to indicate the consistency of the process or to assess potential deviations in the quality of the API itself. In addition the critical reaction parameters should be evaluated. Ideally the critical parameters are identified in the development report prepared prior to process validation but may also be based on experience for well established processes. In nearly all cases specification limits for the critical test results are in place. Therefore the first evaluation would consider the <u>failure</u> frequency to meet such limits. In addition any trends in data should be evaluated across the batches produced during the review period. Appropriate statistical tools may be used to assess process capability when data from a large number of batches is being reviewed. An example of these statistical tools can be the establishment of key performance indi-

	cators. Where the data concludes that there is a drift in process capability, actions should be determined to evaluate the causes and improve performance in the forthcoming review period. The review of all batches which fail to meet specification and the review of critical deviations should look specifically at recurring causes and identify appropriate actions to reduce the frequency and improve performance. Common causes for batch failures and recurring deviations are (this list should not be regarded as complete): • Equipment not functioning correctly or in need of maintenance or replacement. • Inadequate batch instructions or training of operators. • Process parameters so tightly defined that the equipment is not capable of routinely achieving the acceptance criteria. • Inhomogeneous product or inadequate sampling procedures. • Poor quality raw materials or lack of control of raw material suppliers. The impact of changes (see chapter "Change Control") introduced to the processes or analytical methods should also be carefully evaluated to look for any direct affect on the critical test results <u>and the process validation status. The impact of cumulative changes, not just the individual impact of a given change, should be considered when reviewing the impact of changes during PQR's.</u> In a similar way any trends in the stability monitoring program should be reviewed against changes introduced to the processes or analytical methods. Any trends indicating deterioration of product which could affect the retest period or expiry date of the API should be identified and an investigation into the causes should be performed. The status of quality related returns, complaints or recalls should evaluate the adequacy of corrective actions and any trends which require further investigation.
2.51	Based on the Product Quality review a list of clearly defined corrective actions and recommendations should form the basis of the objectives for the product in the forthcoming period. This should include the possibility of process revalidation where significant changes or alterations in the trends of the key quality data indicate this is necessary. Senior management should be involved in reviewing the recommendations and in providing the necessary resources and priorities to ensure the corrective actions and recommendations are implemented.

Chapter 3 Personnel

General Remarks

The environment must encourage and recognise excellence. Staff must understand how they can influence quality, GMP compliance and contribute to improvement.

Staff at all levels must be competent and be effectively managed.

3.1 Personnel qualifications

3.10	For the first time there is a requirement that <u>everyone</u> involved in the manufacture of

	intermediates and API's needs <u>education</u> (schooling) appropriate to the task to be performed. This education needs to be supplemented by training and/or experience in the particular task to be performed.
3.11	It is stated in section 3.11 that the responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing. This can be accomplished either in a generic way for a group of personnel e.g. warehouse personnel or operators in chemical production. For persons having a more specific responsibility, e.g. supervisors, process engineers, it might be more proper to have individual responsibilities laid down for instance in a function description. A possible way of indicating this is to use a matrix in which the responsibilities are defined. Another way of doing it could be the use of separate columns in a process flow chart indicating which unit or function (person) is responsible for what action. Another way of defining responsibilities is within the quality management system documentation - either in terms of which functions are responsible for activities or which personnel undertake specific tasks. Mixture of any of these can be used so long as the quality critical responsibilities defined in Section 2 are suitably documented. Job descriptions or function descriptions should identify the main purpose, role dimensions, outputs/responsibilities, reporting details and required competencies. These should be reviewed regularly.
3.12	Training should range from basic "induction" training through to job specific training. Employees should receive initial GMP awareness training as well as more focused training (e.g. document management for those involved in document control functions.) <u>GMP refresher training should be conducted at least annually.</u> Training in particular operations that the employee performs might be carried through under supervision by a person qualified by education, training and experience. Before a person is allowed to sign a particular operation in the batch record he should be qualified by education or should have received appropriate training. GMP training should be scheduled regularly and conducted according to a plan. Trainig records should indicate the • names of the people trained, • subject of training in keywords • date of training • name of trainer If procedures are revised or newly released the need for appropriate training should be assessed. Effectiveness of training can be verified by direct (e.g. testing, questionnaire) and/or indirect means, e.g. individual observations, periodical assessment (usually annual) interview with supervisor or Internal Audits. The need for GMP training should be periodically evaluate, conducted if needed and documented as part of the individual training program of the employee. Each company should define it based on their own training policy, the performance of each employee and his/her job.

3.2 Personnel Hygiene

The intention of this chapter is to protect personnel as well as products. The type of protection garments for each chemical operation may be given in the production or safety instructions. These instructions should be followed and checked.

Personal hygiene should also be practised by maintenance staff, contractors, visitors, consultants, and inspectors as appropriate.

People not trained in the departmental Hygiene and gowning procedures can only enter the department if accompanied by an authorized, trained person. The decision on the impact of a person suffering from an infectious disease on the job and products can be decided in a combined decision between the supervisor and the occupation health practitioner.

3.21	1) If gowning instructions are required protect the API from contamination from the environment these instructions must be written in a controlled document. 2) For aseptic sterile API manufacturing the Personnel requirements as described in the Annex 1 of the Eudralex vol. 4

3.3 Consultants

3.30	–
3.31	–

Chapter 4 Buildings and Facilities

4.1 Design and Construction

It is important to realize that API manufacturing plants are designed and constructed in various different ways depending on the chemistry, the nature of the API, the location of the plant (country, climatic region), GMP philosophy of the individual company etc. Also it is obvious that existing ("old") plants and "state of the art designed" (new) plants are expected to be very different in design and construction. It was for this reason that the EWG did not give detailed instructions on the design and construction of API plants. However both types ("old" and "new" plants) should comply with the principles of this chapter, however they might be approached in a different way.

The design and construction of "new" plants reflect usually the tremendous increase of GMP understanding and principles which has been taken place in the API producing chemical industry during the past years. The ISPE Baseline Guide for New Facilities Volume 1 Bulk Pharmaceutical Chemicals (June 1996) is well known as a useful reference. However, it has to be pointed out that ISPE uses a different cleanliness concept to that given in the EU, GMP-Annex 1 and ISO 14644 guidelines. It should also be noted that all literature references made in this guide (especially references to air handling systems / requirements) reflect U.S. standards which may differ from European requirements. Each individual company has to decide on the necessary requirements based on their business, quality and processes.

It is expected that compliance with this chapter for "old" plants (in which API's and intermediates have been produced for many years and which have been frequently inspected by the health authorities in conjunction with various applications and marketing authorisations) can be partially achieved by organisational measures (SOP's), but to comply with Q7a 8.52 it may be necessary to upgrade existing plants to give the required level of protection. A "gap" – analysis is a suitable method to identify additional measures (design or organisational) to bring "old" plants into compliance and also appropriate retrospective qualification is recommended.

4.10	An increase of product protection is expected from early steps to the final API, especially for areas where open handling of the API without further purification is performed (e.g. drying, milling, weighing and packaging etc.). In principle there are two options to achieve this goal: Open systems (products are handled temporarily in the open environment) or closed systems. If open systems are applied, a product could be exposed for short period of time (e.g. sampling from a vessel, change of a container during discharging of a centrifuge etc.) or for long period of time (milling, weighing and packaging operations, open filtration, discharging of a tray dryer etc.). This should require different levels of protection. For short term exposure additional procedures may be necessary (e.g. "Only one operation with exposure to the environment at the same time", "Appropriate clothing requirements for the personnel", etc.) to minimise potential contamination. For long term exposure a suitably installed (e.g. according to ISPE Baseline Guide "Commissioning and Qualification") and well maintained air handling systems could ensure the necessary protection.

	<u>Some other precautions include:</u> – Spatial separation – protecting equipment during open product handling (e.g. covering, glove boxes, isolators etc.) – Design of piping (should <u>not be</u> located directly above open manholes, discharging devices etc. unless appropriate protecting measures are in place – Filtering of process gases and solvents For closed systems in general no additional protection is necessary. The integrity of a closed system is not compromised by sampling operations provided appropriate measures are taken to prevent contamination.
4.11	This specific requirement is of particular importance in multi purpose plants with variable equipment.
4.12	Reactors, fermenters, crystallisers, distillation columns, tank farms, storage containers or other closed equipment may be located outdoors, provided there is no need to protect from weather influences. Also not permanently installed equipment (e.g. bulk containers, etc.) may be stored outside, if adequately protected.
4.13	Sometimes (especially in “old” plants) crossing of material or personnel flow can not be avoided. In this instances additional organisational measures (SOP’s) should be implemented to ensure prevention from mix-ups and contamination.
4.14	Other control systems can be computerised material management systems. Quarantined and released materials (API's , raw materials, intermediates, could be stored in the same area (but no mix-up's on pallets etc.), provided their status is clearly indicated and/or traceable (labels, computer status) and procedures are in place to avoid unauthorised use. For safety reasons separate storage facilities may be required for classes of materials with hazardous and /or unstable chemical or physical attributes. Separate production areas are required for certain materials (see 4.4)
4.15	-
4.16	Analytical measurements (e.g. conductivity, pH, density, N-IR, chromatographic methods) need not necessarily be carried out in separated (laboratory) areas, e.g. in case of online analyses.

4.2 Utilities

4.20	Only applicable for critical utilities which are commonly identified by the manufacturer as part of design during risk assessment of his processes. In general only utilities which are in direct contact with the product e.g. steam distillation or nitrogen blanketing, or in contact to the inner surface of equipment. When using compressed air with direct product contact it is recommended to use oil free systems. The frequency of monitoring will depend on the use of the utility and may range from daily (e.g. even online) monitoring to spot checks (e.g. intervals up to once a year) on systems which are carefully maintained. The frequency of testing may be reduced once the company has justified this based on historical data.

4.21	Appropriate only if open systems are used (reference to 4.12). If open systems are used the "ISPE Baseline Guide for New Facilities Volume 1 Bulk Pharmaceutical Chemicals (June 1996)" provides useful information (reference to 4.1).
4.22	Appropriate measures may be e.g.: • selection of suitable filters (and appropriate change of them) • mixing of returned air with fresh filtered air • clean up time (e.g. verified by particle measurements) on product change; including cleaning or changing of filters.
4.23	Although it is required that permanently installed pipework should be identified, this requirement should be limited to pipework dedicated to a particular medium. Other permanently installed pipework (e.g. connection panels for various solvents and reagents) could be generically identified (e.g. 1R22 to 0R14, a connection between two different reactors). Pipework for waste (gases, liquids) should be designed and appropriate located to avoid contamination (e.g. vacuum pump, cyclones, scrubbers, common ventilation pipework from reactors/vessels). Back pressure (non-return) valves can be considered as can swannecks. Draining valves should be installed at the lowest points. During design, methods of cleaning of pipework should be considered.
4.24	-

4.3 Water

4.30	Develop a rationale as to what water quality is sufficient and/or which measures may need to be taken to ensure API quality. Suitability depends on the stage in manufacture, intended route of administration or the nature of the API. Evidence should be available that the water used does not negatively affect the product quality.
4.31	Water quality should be monitored by the supplier and the results be reported to the API manufacturer on a routine basis. Additional in-house testing and monitoring should be considered by the manufacturer according to a predefined and approved plan (including point of use testing, sampling frequency) against predefined specifications that ensure a safe and sound quality of the API (usually meeting guidelines for potable water, unless otherwise justified). Potable water may be even more suitable for use than treated (softened) water due to measures taken to limit microbial growth.
4.32	It is the responsibility of the manufacturer to define the specifications of the water quality by himself to assure the quality of the API. The assessment should take into account the intended use and the final purification step(s) of the API. The CPMP and CVMP "Note for Guidance on Quality of Water for Pharmaceutical Use" should also be considered during this assessment (if the API or the resulting Drug Product is distributed within the EU).
4.33	Validation principles (chapter 12) and change control (chapter 13) need to be applied.

4.34	Microbiological testing should consider both suitable online monitoring (e.g. TOC) and point of use testing. Endotoxin testing is carried out offline and the LAL-test is recommended.

4.4 Containment

4.40	This paragraph is limited to penicillins and cephalosporins. Because they may cause anaphylactic shock at very low levels and contamination with these types of materials can only be avoided by use of dedicated facilities.
4.41	-
4.42	For certain APIs (see 4.40 and 4.41) it may be appropriate to use dedicated or disposable clothing and dedicated equipment including tools for maintenance within the area. Specific clothing requirements should apply to all personnel e.g. maintenance staff, visitors, etc.. Facilities for changing clothes or showering should be considered and special hygiene practices should be applied.
4.43	The comments made on 4.14 should be applied however the storage of closed containers in a common area can be accepted.

4.5 Lighting

4.50	Should comply with National regulations (e.g. Health & Safety).

4.6 Sewage and Refuse

4.60	Disposal has to be performed according to National law. In order to prevent misuse it may be necessary to ensure physical destruction, e.g. incineration of certain APIs, e.g. narcotics.

4.7 Sanitation and Maintenance

4.70	It has to be pointed out that there is a significant difference between a finished dose manufacturing environment (physical processes) and a chemical plant, where aggressive and corrosive reagents may be used. This significant difference should be considered in defining "clean condition". Level of cleanliness required may change from a closed to a open system, also depending on the stage of manufacture. The closer to the end product, the cleaner the production environment should be. Management should assign adequate resources to ensure a good state of cleanliness and maintenance in APIs facilities. Additional guidance may be found in the ISPE Baseline Guide Volume 1, "Bulk Pharmaceutical Chemicals" (June 1996) Defined areas for the storage of temporarily used equipment and its status, (cleaned, identified and protected from the environment), should be available.
4.71	Cleaning of accidental spills and also routine cleaning programmes should be defined. External contractors are often used for sanitation and facility cleaning activities. They should be trained in GMP and their responsibilities defined in a contract (see chapter 16).

4.72	It is not recommended to use these toxic materials in areas where open product handling occurs.

Chapter 5 Process Equipment

5.1 Design and Construction

5.10	The ISPE baseline guide volume 5 “Commissioning and Qualification” gives a very pragmatic system to ensure that systems are “fit for purpose”. This guide recommends undertaking an assessment to separate critical equipment from non-critical. An example would be that cooling water services should be designed according to Good Engineering Practice (GEP) while the temperature probe used for a critical processing parameter should be fully qualified (Qualification: reference to chapter 12.3) using an enhanced design review.
5.11	Materials of construction should be indifferent towards the process materials in order to minimise potential reactions of such materials (e.g. iron with salt solutions giving rust) to avoid formation of impurities that could adversely affect product quality. It also means that the materials should not shed extraneous matter into the process and they should not leach materials into the process. Some forms of polymer or filter cloths would be examples of this type of material.
5.12	If equipment has been qualified over a narrow range and is capable of operation over a wider range then before use it should be re-qualified over the wider range. Most manufacturers design equipment for use in multi-product facilities. From this perspective it would be advisable to purchase equipment that has versatility and is able to cover a wide range of requirements. It should be ensured that the equipment is able to operate correctly for each particular process. (Reference: Chapter 12.3, PQ). An example of this may be a temperature probe that can monitor temperatures over a range –20 to 150 °C but that can also be tuned to enable a reaction temperature of just +/-2 °C to be accurately monitored without the tolerance of the instrument being greater than the range.
5.13	Major Equipment can be identified using as built Pipe and Instrumentation Drawings (P&ID's) with pipes also identified in the plant as well.
5.14	An approved list of lubricants etc can help to ensure that the correct materials are used. Each material should be reviewed for chemical content and potential quality impact. The FDA web page (http://vm.cfsan.fda.gov/~dms) can be searched for approved food grade materials. These can also be specified to equipment vendors during design of new equipment. Increasingly dry seals for agitators are being used to overcome this type of issue.
5.15	This statement particularly applies to the final steps and isolation of the API. For most chemical synthesis this would be a safety requirement in any case. It needs to be stressed that there are no requirements for room specifications for non-sterile APIs at any stage of processing. It is prudent however to increase precautions as the final API step is approached. Early steps requiring materials to be charged in an open plant (inside) environment may also require controls but only for operator protection provided basic cGMP control is in place. See also Chapter 7.4 for additional advice for sampling activities.

5.16	As built drawings should be maintained and updated as part of change control. Failure to do this could lead to safety and quality issues.

5.2 Equipment Maintenance and Cleaning

5.20	A good preventative maintenance program is very important in reducing the number of equipment breakdowns that could cause impact upon product quality, schedule and maintenance costs. This is particularly important for critical equipment that needs regular attention to prevent failure.
5.21 to 5.26	See the APIC Documents "Cleaning Validation in Active Pharmaceutical Plants – Policy, 1999" and "Cleaning Validation in Active Pharmaceutical Plants – Guidance" for practical advice on this subject. (http://apic.cefic.org , "publications").

5.3 Calibration

5.30	Many companies make the mistake of allowing engineers to classify any measuring device as a critical device. Each device should be reviewed to assess what the impact would be of failure or incorrect readings. <u>Classifying instruments as:</u> critical GMP- CPP (critical process parameter) or CQA (critical quality attributes) controlling equipment, GMP = direct quality impacting, GEP – indirect or non-quality impacting. Undertaking this task will allow the critical measuring equipment to be very tightly controlled and not submerged by the vast numbers of instruments that are used within an API site. Many companies use outside agencies for calibration. The equipment user is responsible for ensuring that the outside agencies are competent to undertake the calibration to the appropriate standards.
5.31	This applies more specifically to critical instruments.
5.32	As per document retention requirements in section 6.
5.33	A very good approach is to calibrate prior to start up and then at defined intervals according to the history of calibrations built up with experience. A good idea when starting is to have regular reviews of such data to collect supporting data to define appropriate calibration frequencies (shortened or expanded, based on collected data and experience), re-evaluation periods etc. These reviews are also a very helpful tool to observe any trend and therefore to be able to react before instrument failure occurs.
5.34	A procedure should exist to ensure that instruments not meeting calibration criteria are not be used. It is for this reason that tolerance ranges and calibrations should be appropriately selected for the process to ensure that non-impacting failures of calibration criteria are not routinely observed.
5.35	As mentioned the calibration of critical instruments must be appropriate to prevent unnecessary non-added value investigations into minor failures that could never impact upon quality.

5.4 Computerized Systems

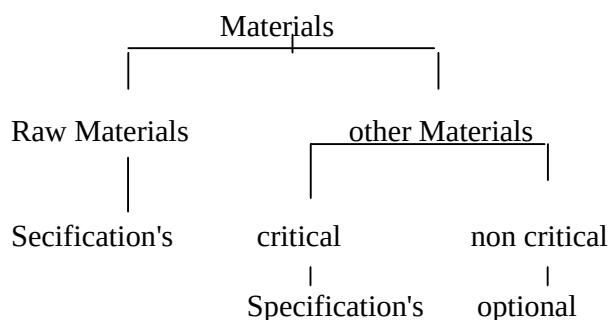
Computerised systems have a very high profile and require an extremely thorough validation approach. It is an area of high inspector interest especially for suppliers of the US market. Reference: Computer validation guideline by APIC will be available and this provides some pragmatic guidance in an area which often involves large amounts of paperwork with too often distressingly low value. Another reference is GAMP 4 (issued by ISPE; http://www.ispe.org)	
5.40	The validation assessment system defined by the ISPE is also a very useful analysis technique to use so that resources and effort are appropriately targeted on critical systems.
5.41	IQ and OQ of computer hardware and software are often treated entirely separately from equipment IQ/OQ. It may be very advantageous to combine the two especially when the two are intrinsically dependent or linked.
5.42	This is a very good approach in that commercially available software by the nature of economic viability and wide-scale usage will reasonably have determined whether the software is fit for purpose. The GAMP guidance is very useful in determining the testing requirements.
5.43	Basic security measures such as access control and user passwords will enable most systems to operate in a compliant manner. Electronic date, time and user stamps are becoming more and more prevalent as industry becomes familiar with the requirement for audit trails. A common problem however is that the audit trails are poorly designed and do not allow searching on the basis of reason for change, date, operator etc. This area is a very significant area of interest for inspectors.
5.44	Similar requirement for all systems, procedures must exist so that personnel can be trained accordingly and these standard operation procedures have to be followed by the operators. This is a basic requirement of system validation.
5.45	Where a second operator is used it does not mean that the operator must watch the figures being entered just that the value should be checked. Double data entry where the system checks each entry against the previous entry to ensure there has been no transcription error. This has been found to be a very effective error reducing mechanism.
5.46	This is analogous to equipment logs. Again some form of categorisation and system should be used to ensure that non-value added or non-quality impacting information is not being collected and investigated
5.47	Change control should be appropriate to the criticality of the system. GEP systems should not require quality review.
5.48	For critical systems a back up system should be available. A server system with automatic back up is ideal but read only CDs can be as effective. It should be noted that it is very difficult to make local PC systems secure.
5.49	Digital readouts etc. can be documented manually or by use of chart recorders.

Chapter 6 Documentation and Records

6.1 Documentation System and Specification

6.10	–																		
6.11	Regarding revision of documents, the company should define e.g. in a SOP when and how documents are revised. Issuing a new table listing all existing documents/SOP'S after a defined period of time (not necessarily 2 years) is acceptable. A useful way to demonstrate that documents have been reviewed and revised is to prepare a report on periodic basis that lists all the documents that have been changed and reissued. The revision history of the document shall be traceable over the retention period. Where electronic document management systems are used the details of the document history can be retained in the metadata and so does not have to appear on the document itself.																		
6.12	Suggested minimum retention periods: <table> <tr> <td>- general production, analytical, control and distribution records</td><td>7 years *</td></tr> <tr> <td>- clinical batches for an IND or NDA (see also chapter 19)</td><td>LC + 1 year</td></tr> <tr> <td>- batches for bioequivalence testing</td><td>LC + 1 year</td></tr> <tr> <td>- product development reports</td><td>LC + 1 year</td></tr> <tr> <td>- development and validation reports of analytical test procedures</td><td>LC + 1 year</td></tr> <tr> <td>- process validation reports</td><td>LC + 1 year</td></tr> <tr> <td>- equipment IQ, OQ and PQ reports</td><td>LC + 1 year</td></tr> <tr> <td>- supporting systems (e.g. utilities, computerised systems)</td><td>LC + 1 year</td></tr> <tr> <td>- training records</td><td>7 years</td></tr> </table> (for clinical trials and demonstration batches LC + 1 year should be considered) Note: LC means "life cycle" of the product where shelf life is included. "Life cycle" means the process starting with the user requirements, continues through design, realisation, qualification, process validation and maintenance until the stadium "status" of not in use. * after the date of the record	- general production, analytical, control and distribution records	7 years *	- clinical batches for an IND or NDA (see also chapter 19)	LC + 1 year	- batches for bioequivalence testing	LC + 1 year	- product development reports	LC + 1 year	- development and validation reports of analytical test procedures	LC + 1 year	- process validation reports	LC + 1 year	- equipment IQ, OQ and PQ reports	LC + 1 year	- supporting systems (e.g. utilities, computerised systems)	LC + 1 year	- training records	7 years
- general production, analytical, control and distribution records	7 years *																		
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- batches for bioequivalence testing	LC + 1 year																		
- product development reports	LC + 1 year																		
- development and validation reports of analytical test procedures	LC + 1 year																		
- process validation reports	LC + 1 year																		
- equipment IQ, OQ and PQ reports	LC + 1 year																		
- supporting systems (e.g. utilities, computerised systems)	LC + 1 year																		
- training records	7 years																		
6.13	(1) Could you present an illustrative example how the entire LC (Life Cycle) is defined / calculated / used within the attached section 6.13 of the HOW TO DO interpretation / document ? (2) Is there a contradiction regarding retention periods of i.e. All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with test dates, records should be retained for at least 3 years after the batch is completely distributed. as described in section 6.13 of the ICH Q7 guideline compared to the respective HOW TO DO interpretation / advice summarized section 6.12 general production, analytical, control and distribution records: 7 years* (* after the date of the record).																		
6.14	No pencil, no white out and no crossing out and no obliteration of an original entry that is subsequently corrected.																		
6.15	–																		
6.16	–																		

6.17



Item	Type of Specification
API Starting Materials,	Internal specification mandatory. More details may be needed compared to RM. Pharmacopoeia requirements grade materials are not needed.. unless necessary to control the quality of the final API
Raw materials	Internal specification mandatory. Pharmacopoeia grade materials are requirements not needed unless necessary to control the quality of the final API
Intermediates	Internal specification optional. Pharmacopoeia grade materials are requirements not needed. unless necessary to control the quality of the final API
API's	Pharmacopoeia mandatory. For non-compendial APIs refer to Q6a. Additional internal specifications optional if stipulated by customers.
Labelling	Pharmacopoeia and internal specifications mandatory concerning text of labels. Material specification optional.
Packing material	Printing see labelling. Material specification mandatory.
Process aids including utilities (product contact materials)	If such materials are critical, the use of internal or public specifications (e.g. technical standards like ISO, EN etc.) is advisory.

	IPC	In order to avoid the necessity of doing OOS-Investigations on deviating in-process controls, ranges need to be established. It is my understanding that no OOS is required on IPC tests without restrictions – i.e. whether you set a range or not – e.g. by defining upper / lower control limits and action limits for the purpose of process monitoring. It is recommended to mention this exception in the applicable SOP.
6.18	–	

6.2 Equipment Cleaning and Use Record

6.20	It is recommended to use a log system (but separate records would also be acceptable (different documents) for the chronological record in order to see: - for which purpose and batch the equipment has been used - from whom and how (cleaning method used) it has been cleaned (when appropriate) - any maintenance that was done referring to who did it, what and how it was done (a reference in the batch record should be made, if maintenance was performed during production). - the status before and after maintenance, even when the equipment was found to be o.k. This requirement is valid for major equipment only (ref. 6.52). Not sure that 6.52 in the How to Do document has an obvious statement to make to this clause. Do you mean ICH Q7a clause 6.62 as opposed to the HTDD clause 6.62. Perhaps we need to make these cross references clearer? It is important to describe the exact type of repair of the equipment in the record. Status of equipment should be recorded and checked. Status of cleaning and maintenance should be recorded and checked, preferable in a log. Cleaning and maintenance may be documented in a database (electronic records) which then should comply with section 6.10 and 6.18. So these are Q7a references as we have made no observations in the HTDD against these clauses.
6.21	A plant or unit log instead of individual equipment records should also be applicable if the equipment is firmly incorporated into a plant or unit (installed and piped for permanent use) even if this plant/unit is not dedicated but used for production of different API's in campaigns. If the records of cleaning, maintenance and (re)use are included in the batch record, it may be recommended that this information is written on the first pages and that critical entries are double signed. The review of the batch record will then be easier. If the cleaning and maintenance records are not part of the batch record, a reference to

	the appropriate documentation or database should be placed in the batch record. The objective of this record keeping is to trace what particular equipment was used in manufacturing (see glossary of Q7a) a particular batch and what status it had at the time of usage.

6.3 Records of Raw Materials, Intermediates, API Labelling and Packaging Materials

6.30	The objective of this record keeping is to trace the above Materials back to the suppliers production records and trace forward until the API-batch delivered to individual customers in case of any failure occurring in the supply chain. The responsibilities for a final decision regarding rejected raw materials etc. should be defined in a procedure.
6.31	The approved master of a label need not to be a label itself but may consist of a approved set of relevant data used by or sent to a label printer. A 0-copy of the label may be filled together with the batch record to proof compliance with such master.

6.4 Master Production Instructions (Master Production and Control Records)

6.40	Review and signing by two people is sufficient but not restricted to that number. . One should be in the Quality unit. The review has to be performed by the people/functions appropriate for this task. This may involve R&D, QC, Production, engineering and probably also regulatory affairs as well as SHE (safety, health, environment) departments.
6.41	It is possible to use, at different production locations, different Master Production Records derived from the same basic receipt. template(?) / recipe?.

6.5 Batch Production Records (Batch Production and Control Records)

6.50	The third sentence may refer to the situation that a company, e.g. for business reasons, has the possibility to manufacture a product in different batch sizes, always using the same basic recipe. This recipe then is the current master production instruction.
6.51	-
6.52	• For deviation reports: see comments on 8.15 • Identification of equipment: see comments on 6.21 • Double signatures of performing and checking personnel: see discussion on witnessing under 8.12 • Yields: see comments on 8.14 • Packing and labelling of intermediates is only applicable if prolonged separate storage of such materials occurs, e.g. batch production starting from warehouse stocks. I would say if ANY separate storage of intermediate or API should include evidence that suitable controls have been applied to avoid mix ups and mistakes. If this means keeping a copy of intermediate labels as for final packaging then that would be fine. •
6.53	An investigation has to be set up at every critical deviation when the origin of the deviation or when the impact on the product quality isn't known. A SOP on investigations of critical process deviations should define what is to be understood by critical. Compare other (related) batches with the same deviation. Use of the principles in ICH Q9 (Quality risk assessment) is a very useful way to classify critical deviations

6.6 Laboratory Control Records

6.60	Graphs, charts and spectra can be added to the control record or can be stored separately. In the latter case these documents should be easily retrievable. These documents should be signed and dated by the person who performed the test. A reference to the identification of the sample analysed should be included. The secondary review of the original records only needs to be done when the com-

	plete analysis of a sample of a batch has been performed. This can be done on a sheet/record where all results have been summarised
6.61	Modifications of analytical methods should be subject to change control and considered for revalidation prior to introduction.

6.7 Batch Production Record Review

6.70	“Established specifications” can not always be limited to pharmacopoeia specifications, also additional in-house specifications could apply.
6.71	During a batch record review check for • missing records and out-prints • incomplete entries • illegible corrections • equipment maintenance, breakdown and replacement • valid calibrations and service intervals of test equipment (as a useful cross check to routine control of test equipment) Not sure about this. See HTDD 8.15 where process deviations on this topic are listed. In batch production review we would not ask for nor seek verification of the calibration status of equipment. This is part of the ongoing QA system which would be expected to be compliant in routine cases. Else why stop here? Why not check analyst and production staff training records at the same time? • reports on OOS-results • completeness of deviation reports • impact of reported deviations on product quality These ought capture calibration issues as HTDD 8.15 suggests • compliance with specifications, parameter ranges or acceptance criteria including tighter customer specifications • usage decision
6.72	See comments on 6.71 and 8.15
6.73	—

Chapter 7 Materials Management

7.1 General Controls

All activities from receipt till approval or rejection of materials should be described in one or more procedures. Materials must be purchased against agreed specifications.

Companies should prepare a list of critical raw materials based on good scientific rational and impact on the quality of the API. Suppliers (manufacturers and/or agents if applicable) of critical materials should be evaluated and approved by the quality unit. The evaluation can be based on

- historical experience with the supplier,
- on a questionnaire,

- checking/comparing own analytical results (for e.g. three batches/shipments) with those on the suppliers Certificate of Analysis and / or
- an audit done by a person authorized by the purchasing company
- use test

Audits are not mandatory as per current GMP and should be considered on a case by case basis for example if deviations are observed. Other useful information can include the reputation of the supplier within the industry and the availability of certificates such as ISO-9000 certificates. The evaluation and approval process should be described in a procedure, taking into account some or all these possibilities. This includes the fact that the name and address of the manufacturer of a critical material must always be known. A change of the source (e.g. manufacturer or supplier) of a critical material should be handled according to the Change Control procedure.

7.2 Receipt and Quarantine

Before acceptance of incoming materials the packaging should be checked visually. The materials should be sampled, tested and released. As long as the material is not released it must be held under quarantine; this can be realised in different ways e.g. separate areas or through a validated computer system. These systems or others may also be used to identify the status of the material.

Incoming stock materials should be released before mixing them with the existing stock. This new stock should get a new lot number.

Non-dedicated tankers should be checked for cleanliness before use to prevent cross-contamination. Ideally, a cleaning certificate should be provided with each supply. If no such certificate can be provided, an audit of the cleaning procedure of the suppliers and/or transport company is recommended.

As in the factory, large storage containers and possible appendages should be identified appropriately.

7.3 Sampling and Testing of Materials

Sampling plans should be scientifically sound, not necessarily statistically based, but appropriate to the material being sampled and easy to use. The importance of obtaining a representative sample for analytical testing is critical. The quality/accuracy of the analytical data obtained is dependent on how representative the sample is.

Sampling plans must consider not only how the raw material is manufactured but the use and criticality of the material. As a consequence, sampling plans may be different for different materials, and grouping of materials in different sampling methods is commonly used. A risk based assessment approach can be used to support and justify the most appropriate sampling plan.

Examples of parameters which may be evaluated during a risk assessment are:

- Criticality of the material
- Manufacturing and supply process: manufacturer and/or agent controls
- Manufacturers/Suppliers quality systems
- Packaging controls
- Historical data
- Homogeneity

Manufacturing and Supply Process/Homogeneity

Knowledge of the raw material manufacturer's process is important in determining the appropriate level of sampling. Factors to consider are, whether the material has a final processing step that ensures the material is homogeneous and/or whether the manufacturer has homogeneity data for the current process of the concerned material. If the material is homogeneous then the need to sample from multiple containers and test a number of samples may not be required. Homogeneity data may be obtained from the supplier or generated in house. If it is not homogeneous (or knowledge is not available) then there is a risk. In this case the use of the material should be considered to determine the necessary level of sampling and testing for example top, middle and bottom of the containers. Take for example the scenario where a material that is not potentially homogeneous with respect to water and the level of water in the material can impact downstream processing. If one container is used at a time in a process, then every container may need to be tested, but if all the consignment is used in one batch of the process then a testing of a composite of the batch to give a mean representation of the batch made up from all the containers may be more appropriate.

Knowledge of the raw material manufacturer's process is not the only information that is needed; subsequent packaging and handling operations should also be considered. For example, consider the scenario where a process produces homogeneous material product but downstream packaging or drumming introduces the potential to desegregate it - this would impact sampling plans.

Another factor to consider is if agents/repackaging operations are used in the supply chain. If agents are used then knowledge of their quality systems, operations and practices must be considered. For example, the risk from an agent or distributor that repackages a material is potentially greater than that of an agent who only holds and distributes the material in the original packages/containers.

Issues of homogeneity can usually be ignored for low viscosity liquids.

Supplier's quality system

Knowledge of the supplier's quality system is also important. Quality systems are used to support the quality and integrity of the product. Any reduced sampling plans should only be applied to vendors who have adequate quality systems as one of the major concerns for supplier evaluation is to consider the potential for product contamination.

An understanding of the process, facilities and potential for cross contamination needs to be known and considered. For example, if material is received direct from a manufacturer that only produces one product, then the risk of cross contamination is less than from a supplier using dedicated equipment in a multi purpose plant. This in turn is less than from multi purpose equipment. Consider the scenario where a solvent is manufactured in a dedicated facility, but is drummed in a multi purpose one rather than a dedicated drum filling facility. For the latter, sampling of any drum should give a representative sample for testing but in the former scenario, if the drum filling order is known, sampling and testing of the first drum may provide more appropriate analytical data relating to potential batch contamination.

Review of the suppliers packaging and labelling controls is beneficial as this can be used to

support review of the labelling of incoming deliveries as a system for identification purposes.

Information on the quality systems can be obtained via an audit of the supplier or via an appropriate vendor questionnaire. The questionnaire should contain the relevant questions to allow an assessment of the supplier's quality management system. Other information can support this for example ISO certification or confirmation of a successful regulatory audit.

Historical data

Previous quality knowledge of the manufacturer/supplier's deliveries/other materials may be useful data to ensure an appropriate sampling plan is assigned. A review of OOS investigations and complaints can assist.

Criticality of the material

Critical process parameters of a process may be linked to a raw material parameter. This in turn may lead to a need for a sampling plan that ensures this parameter is tested to a different regime to that of the other materials quality attributes to ensure downstream processing is not impacted.

In theory, only after a thorough evaluation during the risk assessment process, should reduced sampling and testing be considered.

Common industry practice is to use $\sqrt{n}+1$ (where n = number of containers) and is widely accepted in many situations even though it has no statistical basis it reflects those statistically based. Other examples of sampling plans are British Standard 6001-1, ISO 2859, ANSI/ASQCZ1.4-1993, derivatives of $\sqrt{n}+1$ in WHO document, http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf (Annex 2 and 4).

Other considerations

If there is a quality issue with a raw material that may impact the sampling plan then increasing the sampling regime can be applied. This may include changing the number of containers to be sampled or even the sampling method for the material. As data becomes available that shows the preventative measures taken by the manufacturer/supplier are controlling the issue then a return to the normal sampling can be reinstated with appropriate justification.

If sampling could have an impact on the integrity of the material, for example hygroscopic substances then less sampling should be considered. These scenarios should be justified and documented. Highly hazardous raw materials which are not sampled and tested before release should be evaluated as per ICH Q7a section 7.32

7.4 Storage

Materials should be stored in a way that the quality of the raw material can not be negatively influenced taking into account light, time, temperature and humidity. Sufficient space should be

available in the warehouses to allow efficient movements without damaging the packaged materials as well as to allow for cleaning. It is good practice to store the material at sufficient distances from walls.

The floor of the warehouses should be easy to clean.

Materials stored in fibre drums, bags or boxes should be stored off the floor e.g. on pallets. Materials (e.g. in steel drums) may be stored outside if their identification remains guaranteed and if the material is not adversely affected by such storage conditions. Before opening these containers they should be cleaned appropriately.

7.5 Re-evaluation

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Chapter 8 Production and In-Process Controls

8.1 Production Operations

8.10	Weighing or measuring of raw materials (solids and liquids) should follow procedures designed to ensure accuracy and to avoid cross contamination. These may include: • Specified weighing or measuring areas protected from the environment with controlled access. • Use of log books or registers to record the usage and cleaning of the weighing, measuring area. • Cleaning procedures for the weighing ,measuring areas • Procedures to ensure that materials for different processes are not dispensed concurrently • Extraction systems to control dust or vapour exposure during dispensing • A range of appropriately scaled weighing or measuring devices should be available to ensure accuracy of weighing operations. The appropriate scales for specific weights or measures should be defined. • Flowmeters, for liquids, or weight belt feeder, for solids, may be appropriate for charging or for monitoring continuous production processes. • Critical weighing and measuring devices should be appropriately calibrated and traceable to certified standards. The calibration should be recorded and performed on a regular basis. • Regular checks and records by operational staff that balances are functioning correctly should also be considered.
8.11	Examples of suitable primary container for sub-dividing solids are • a plastic bag for smaller quantities or • plastic bags, liners inside rigid support, or • loading hoppers for quantities of solids.

	Multi-use containers receiving sub-divided material (e.g. loading hoppers) should be clearly identified. Such equipment should be appropriately cleaned according to written procedures.

8.12	Companies should define the critical weighing, measuring or subdividing operations which should be witnessed or subject to an equivalent control to the minimum number. Don't really need this. What you do need is that API companies define "critical" in such a manner that not everything is critical. So only some things are critical and it is these that this should be based on the known critical parameters which could impact on the quality of the API or intermediate. General non-critical weighing or measuring of materials does NOT require witnessing. As was seen in the step 2 ICH Q7a document it was intended that such weighing operations should be "supervised", which would not have required the physical presence of a second person. However the word "supervised" suggests that someone more senior in the organisation should carry out this task. To avoid this interpretation the word "witnessed" was chosen to indicate that anyone could carry out this check. However it was not intended that this word should be used within the narrow legal sense of being physically present throughout the operation and a subsequent check would fulfil the requirement. • "witnessed" = second person checking, not permanently present A typical equivalent control that avoids the need for a second person is a recording system where all weighing or measuring operations are detailed. The critical weights or volumes could be checked at the end of the batch production. The final check by production that the identity and lot numbers of dispensed raw materials comply with the batch instructions may also include a check of the quantities or volumes of critical measurements. These checks should be clearly defined in the operating instructions for each batch.
8.13	Companies should decide which operations other than weighing and dispensing could be considered critical and therefore should be witnessed or subject to additional controls. Examples are : • Charging of critical raw materials. • Control of critical temperatures, pressures, times. • Point of crystallisation of API where this is critical to the control of polymorphs. • Operations that are critical (and thus subject to these controls) should be documented, ideally on the Master Batch Instructions (see 8.15).
8.14	Variation in yield is a likely indication that a process is not performing to expectations. Therefore investigation of variations in yields at defined process steps is intended not only to control variations in production efficiency but also to optimise process consistency and assist in assuring consistent product quality. The expected yield may be defined at designated steps for example key intermediates, the final step of synthesis of the API. It will be easier to calculate the yield of dried products. When wet products or crude liquids are involved, it may be necessary to calculate the yield after analysis and determination of the percentage of expected product. In some cases there could be significant batch to batch variations in yield due to different quantities of product remaining in enclosed equipment such as filtration or drying equipment. In these cases monitoring of yield trends or averages over a range of batches may be more appropriate.

	Yield definition may also not be practicable in purification steps, continuous production processes or processes with multiple recycle streams (e.g. mother liquors). These processes instead may be assessed for example on a weekly or monthly basis. The important point is that companies should evaluate and document the likely yield expectancy and variability and decide what is the expected yield and the likely impact on quality. Once again there are advantages in defining critical process steps to ensure that the yield investigations are focussed on the steps likely to have an impact on product quality.
8.15	A deviation is defined as a departure from an approved instruction or established standard. The guidelines require that ANY deviation to the defined processing steps in the production records should be documented. It may be useful to have an additional page in the production record to allow easy recording of unexpected occurrence or deviation to the standard instructions. It is then the responsibility of the persons reviewing the completed production records (Production) to decide which deviations could be considered critical and require investigation. The Quality Unit should check the deviation records (not the full production/batch records!) Doesn't the quality unit have to do this as part of batch production record review – 6.7? – OK only has to do the critical steps so perhaps this has to say Quality Unit should check the deviations to see the procedure was followed and CRITICAL deviation records for impact on API quality and ensure that critical deviations were investigated (reference 2.22 and 6.72 ICH Q7a). A critical deviation is defined as a variation to previously established critical parameters or a significant variation to standard operations which COULD affect the quality of the API or intermediate. Critical deviations should always be investigated and corrective actions identified. Corrective actions should be subject to change control procedures. Where deviations recur on a regular basis the need for example to re-qualify equipment, retrain operators, redefine the process parameters or to implement other appropriate actions should be considered. This review may be done as part of the Product Quality Review. See Section 2.5. Examples of deviations are: • Incorrect charging of raw materials • Temperature, pressure, vacuum parameters outside defined limits. • Operating instructions not correctly followed. • Breakdown of process equipment or failure of utilities. • Equipment out of calibration. • Production records not adequately completed. • Temporary alteration to defined production instructions • In Process Control Limits not achieved. • Alternative production equipment used at short notice. • Extraneous contamination of API and intermediates

	Any other unplanned event.
8.16	Defining the process status of equipment is intended to assist the process operators and supervisors to properly control their operations and avoid the miss-use of equipment. In particular the following examples should be well controlled: - The batch number and process in operation - The cleanliness status of equipment - Equipment under maintenance, Out of Service or Out of Calibration
8.17	Colour coded labels for material for reprocessing or reworking may be appropriate. The Quality Unit should clearly identify material for reprocessing or reworking and ensure that the appropriate procedure for reprocessing or reworking has been approved before the production unit consider using these types of material. The appropriate control of materials requiring reprocessing or reworking could be quarantine (see 10.11), computer controlled, specific labelling, locking of equipment or other appropriate measures.

8.2 Time Limits

8.20	Examples of possible deviations of time limits for processing steps are: - extended drying or distillation times beyond what is normally observed due to faulty equipment, - interruption to normal production due to external events e.g. fire alarm or power failure or public holiday. - Use of raw materials or intermediates beyond documented storage times.
8.21	An appropriate storage area for intermediates held for further processing should be defined. The storage area should protect the materials from the risk of external contamination or cross contamination with other materials and from extremes of temperature and relative humidity. Intermediates which will be stored for any significant period should either be tested again prior to use or have a retest or shelf life period established. The retest or shelf life period can be determined by: - Bibliography. - Information of the manufacturer - Based on the experience of the company when re-testing products that have been stored during a certain time. - A simple analytical check of material kept under standard storage conditions. (This does not need to comply with ICH Q1A) Special care should be taken with the storage of wet intermediates, to assess the likelihood of degradation.

8.3 In-process Sampling and Controls

8.30 –	The most common examples of in process controls are:
8.31	pH control, reaction completion, crystallisation, and batch drying checks. In these and other cases the in process control data assists with process monitoring

	The acceptance criteria are not intended to be specification checks unless there is a direct relationship with product quality.
8.32	This approval could be carried out as part of the master production instruction approval.
8.33	Any deviations from pre-established limits for critical in process controls should be investigated and reviewed by the quality unit of ICH Q7a and HTDD.
8.34	Sampling is required to be scientifically sound. This is a common sense approach to a potentially critical procedure. Samples are used to monitor the process and the results of the sample predefines the disposition of the material being processed. The integrity of the sample predefines the integrity of the analysis. Sampling procedures are therefore a highly important part of GMP The importance of sample integrity should not be overshadowed by the focus upon the result. Scientific sound sampling procedures should be developed by considering the following issues: - Sample size: at least enough to undertake check testing if designated a critical test requiring OOS investigation. We said earlier that there is no need for an OOS on IPC tests which is what 8.3 is all about. Can we be consistent? - Sampling method: should be demonstrated to provide representative samples of the whole batch. Particular care is required for sampling of solids and slurries. Simple dip pipes can be used for homogeneous liquids while more complex systems including re-circulation loops may be used for slurries. Sampling of solids is best done from a falling goods stream. Sampling out of bags or drums should be done carefully to ensure representative samples obtained for particle size distribution and analysis when these parameters are critical. - Sampling procedure: should provide sufficient instruction to ensure that truly representative samples are obtained. Details should include flushing, re-circulation and cleaning of samplers (sampling equipment). Particularly for critical steps and sampling of the API itself evidence should be available that the sampling methods allow a representative sample to be taken. Where there is a risk that the batch is not homogeneous for example tray drying of an API a blending step to improve homogeneity should be considered. Although the sampling regime SQR of n+1 is a common but not the only practice within the industry we recognise that other statistical approaches can be suitable Root n+1 is scientifically sound - -it may not be statistically valid but in my opinion it provides a nice point between sample every container and sample only one ISO 2859 Sampling procedures for inspection by attributes is an alternative reference. (see also HTDD 7.3 for details on justifying sampling strategies.
8.35	Sampling tools should be controlled by a cleaning procedure and should be adequately stored when not in use to avoid contamination. Care should be taken to minimise the risk of external contamination during in process sampling. For example in situ sampling probes should be considered when sampling the final API or protective covers should protect the area where the process equipment will be opened. As a minimum the area around the sampling point should be

	well maintained with no evidence of flaking paint, rust, dust or other possible sources of contamination. Procedures should be in place to protect the integrity of in-process control samples, for example: flushing of in situ sampling probes to ensure a representative sample is taken. In process sample containers should be clean, clearly labelled with product name or code, date, time, batch number, step number, operator name, if relevant. Reference: ISPE Baseline BPC Guide Current version is called "ISPE Baseline Guide: Active Pharmaceutical Ingredients Second Edition June 2007.
8.36	In-process tests that require OOS should be clearly identified/designated and these should be critical tests only.

8.4 Blending Batches of Intermediates or APIs

8.40	–
8.41 – 8.42	As written the guidance on blending applies to both chemical and physical property specifications. Where the intention is that each individual batch should conform to both chemical and physical property specifications. Care should be taken when setting specifications for intermediate steps or for API's not to include unnecessary limits if a further processing step e.g.: re-crystallisation as part of the process, milling or micronisation will result in product which complies with the final specifications.
8.43	–
8.44	–
8.45	–
8.46	–
8.47	–

8.5 Contamination Control

8.50	Where significant carryover occurs between batches and particularly in the case of filter or dryer heels, it should be demonstrated that no unacceptable build-up of impurities or, where applicable, microbial contaminants is occurring (see 5.23 ICH Guide). This will also assist in determining the frequency of cleaning of equipment which is dedicated to the long term manufacture of one product.
8.51	A wide range of production facilities exist from modern multi-purpose facilities designed to minimise risk of cross contamination to older facilities which rely on procedural controls to minimise cross contamination. It is recommended that companies review existing facilities and define the controls required to minimise cross contamination particularly as the process moves to the final API isolation. Some of the risks which should be assessed are as follows: Where more than one product is manufactured simultaneously in one production area or building strict procedures should be in force to avoid for example the misuse of

	raw materials and intermediates during processing operations. • Generally such charging areas should be clean and tidy with no evidence of for example flaking paint or rust, or dripping water from service pipework should be in the vicinity of the charge area. • Where intermediate is isolated in open production areas, adequate distances should be maintained between equipment for different processes for example filters or dryers
8.52	These clauses have potentially wide impact on API manufacturers. • Charging of solids and liquids at the final step of API's should be controlled to avoid cross contamination. • Solids loading systems which avoid opening of reactors to the environment may be appropriate for the final API. • .Segregation of the isolation areas for the final API including controlled access by personnel should be considered. • Where the API is exposed to the external environment for example during sampling of the final reaction mixture, off loading of filters or dryers then building controls and procedures should be in place to avoid the risk of external contamination. • No microbiological monitoring of isolation areas and equipment for APIs used in oral solid dosage forms is required unless a microbiological quality is specified. • Classified Rooms, if applicable, and control of microbial contamination are only essential when stipulated by the requirements of the drug product process. They do however offer an engineering solution to the risk of cross-contamination. For additional guidance see HVAC section of ISPE Baseline on Bulk Pharmaceutical Engineering Guide 1996. The key requirement is that building controls and procedures are in place to avoid contamination at any of the steps after purification of the API. The ISPE Pharmaceutical BPC Guide for New Facilities Volume 1 chapter 3 offers detailed guidance on how to assess the risk of cross contamination and defines the options for engineering solutions appropriate to the risk.

Chapter 9 *Packaging and Identification Labelling of APIs and Intermediates*

9.1 General

The focus of this chapter is mainly on packaging and labelling operations of API's and intermediates intended for shipment to third parties and it is not the intention that all requirements have to be met for internal transport at one site under the manufacturers control. Also a lot of requirements are established for pre-printed labels or labels that are printed by on site computer and stored. In the API industry most labels are printed on demand, and therefore these requirements are not applicable.	
9.10	<u>Labelling materials</u>: Applicable only for pre-printed labels or labels that are printed by on site computer and stored. For labels which are printed on demand, written procedures describing the receipt, identification, quarantine, sampling, examination, and/or testing and release, and handling of blank labels - bearing no information at all - are not applicable. (A label is only considered as a label if product or batch related information is imprinted).
9.11	See remarks 9.10
9.12	See remarks 9.10

9.2 Packaging Materials

Appropriate packaging materials to be used should be defined in the master production instruction (see chapter 6.41 for reference). For API's and, when appropriate, for commercially available intermediates the suitability of packaging materials should be supported by product stability testing.	
9.20	Typically most APIs are stored and shipped in fibre drums with polyethylene liners or polyethylene bags. The inner lining or bag in direct contact with the API should be of food grade plastic (if intended for shipment to the U.S.) or comply with local regulations. The inner packaging should be controlled by the company with respect to identity and traceability.
9.21	Industry practice is to inspect these packaging materials for defects and cleanliness. Sanitising containers does not imply sterilisation. In most instances, sterilisation is not applicable for API packaging materials.
9.22	• <u>For the same product</u>: Visual inspection should be enough, effectiveness of cleaning should have been demonstrated (e.g. by cleaning validation). • <u>For multi-use</u>: Cleaning procedure has to be validated, or at a minimum, depending on the stage of manufacture, analytical verification has to be performed. <u>Remarks</u>: Only applicable if product is in direct contact with the surface of the container, and not if in-liners are used (PE bags etc.)
9.3	For the API industry, computer printed labels are a norm and pre-printed labels are exceptions. Most of the ICH statements addressed pre-printed labels. Computer printed labels are typically printed "on demand" basis and little or no storage is

	needed.
9.30	Applicable only for pre-printed labels or labels that are printed by on site computer and stored. For labels printed "on demand" blank roles of label are not applicable. See HTDD 9.10
9.31	The main focus is on pre-printed labels or labels that are printed by on site computer and stored. For labels printed on demand also procedures should be in place to check "number of labels demanded", "number of labels printed", number of labels put on the drums", "number of labels attached to the batch record or other traceable documents, e.g. shipping / dispensing documents", "number of labels destroyed". Additionally a check that the label(s) conform to the master should be documented in the batch record or other dispensing records. (See also chapter 6.52 for reference). Discrepancies referred to should be treated as critical deviations and thus the results of the investigation should be approved by the Quality Unit and include measures to be taken to prevent reoccurrence.
9.32	See comments 9.31, returned labels are not likely to occur if "on demand" printed labels are used. If too much labels have been demanded, they should be destroyed and this activity should be documented in the batch record.
9.33	–
9.34	Programmable printing devices used to print labels on demand should not be subject to validation. Printing devices may be controlled by a template, which may be changed by designated personnel according to an established procedure(s). Should also fall under the change control procedure
9.35	The examination of printed labels regarding proper identity and conformity with a master should be documented in the batch record or other documentation systems in place, e.g. dispensing records. (see 9.44, examination and documentation of packaging and labelling).
9.36	See 9.31 for reference.

9.4 Packaging and Labelling Operations

9.40	Additionally to primary packaging and labelling after completion of production re-labelling with customer specific information as part of manufacture / dispensing / shipment is common practice. These activities have to be documented in the batch record or other systems in place, e.g. dispensing records.
9.41	One labelling operation at the same time, only one batch to be labelled (not to be interpreted as stored) on one pallet or in a defined area (spacially separated). Also bar-code systems correlating batches to labels could be used to prevent mix-ups.
9.42	–
9.43	If the retest date is extended and mentioned on the label, the label must be replaced to reflect the extended retest date.

9.44	–
9.45	Examination results should be documented as described in 9.44 and not necessarily in the batch record, however the documentation could be attached to the batch record, but also other systems which are retrievable could be used.
9.46	It is recommended that company specific seals should be used particularly as imported material are often opened by customs and it should be apparent that such opening and re-sealing has taken place.

Chapter 10 Storage and Distribution

10.1 Warehousing procedures

This chapter covers the storage of all materials. In general all storage conditions should be established based on stability data or suitability for use information. These data can be derived from formal stability studies for APIs. For intermediates and other materials they might be obtained from scientific considerations, product history, published data or from reanalysis of materials stored for some time. Specific storage conditions are very rarely necessary, they only apply for materials with known stability problems regarding temperature and/ or pick-up of moisture in the standard packaging. Advice on storage conditions (specific and unspecific) is given in USP “General Notices, Storage Temperature and Humidity” where also the concept of applying the mean kinetic temperature approach is explained. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the non-isothermal effects of storage temperature variations. (See also ICH Q1a for reference). It is not always necessary to have records of storage conditions. This is only necessary when the stored material could be negatively effected by excessive temperatures or humidity over a longer period of time	
10.10	For APIs not requiring specific storage conditions, ambient temperature may be adequate without the use of monitoring control devices. In cases where storage conditions are critical, monitoring control devices should be appropriately calibrated, and it may be necessary to qualify the warehouse itself with respect to temperature distribution. (for reference, see chapter 12.3 “Qualification”).
10.11	Acceptable separate storage areas for such activities may solely be marked shelving or floor spaces with the exception of areas for rejected or recalled products in which physical barriers should be utilised to prevent unauthorised use, e.g. locked cages, areas or rooms. Alternative systems may be computerised stock control with restricted access. These do not require separated areas.

10.2 Distribution procedures

The focus of this chapter is on shipping of APIs and commercial available intermediates to third parties and not on internal transport and/or transport between different sites of the same company.	
10.20	Distribution under quarantine is only accepted when under the control of the manufacturer of the API or intermediate and not for transport to third parties.

	<u>The following examples are not considered as third parties:</u> • Subcontractors (e.g. processing, milling, micronization, drying etc.) • Warehousing (off site or at a subcontractors site) • Processing at different sites of the same company For subcontracted activities the formal quality agreement should cover this scenario as recommended in Chapter 16.
10.21	Appropriate protective outer packaging and a reliable shipper should be chosen to avoid damage during transport. For sensitive products special shipping conditions should also be specified.
10.22	Only applicable if safety or API / commercial intermediate stability (indicated by stability data) require special conditions and / or instructions. For stable and / or harmless API's normally no specific conditions are required on the label. Independently from GMP's, national and international laws and regulations have to be followed.
10.23	Appropriate transport and storage requirements are typically conveyed to the shipper on the bill of lading. If very special storage conditions are required to avoid alteration, it might be necessary to monitor the shipping conditions.
10.24	Full traceability for all shipments from the manufacturer to its customer(s) has to be in place. If API's or intermediates are delivered to a broker, full traceability has to be ensured by the broker as well according to chapter 17. (<u>Remarks:</u> In this case the final user of the API is unknown to the API producer, therefore full traceability to the end customer should be the duty of the broker).

Chapter 11 Laboratory Controls

11.1 General Control

11.10	The laboratory facilities at disposal of the Quality Unit can be internal or external: – In the Quality Control Department – In the Production Department – At other sites of the same organisation (e.g. company which operates to the same quality procedures) – As contract laboratories, provided they comply with Chapter 16. Whatever the laboratory selected, the responsibilities remains within the Quality Unit of the producer (see 2.22). Design and construction of the facilities (internal or external) have to be in accordance with the type of tests performed (i.e. microbiological tests require sample protection from particulate contamination when handled, the weighing room should not have vibration, ...). Separate rooms for different kind of tests (microbiology, chemistry, powder handling, etc.) can be needed.
11.11	The laboratory should have SOPs describing: • <u>Sampling</u> Different approaches are possible: a general method, different methods grouping products (liquids, solids, dangerous, hygroscopic, ...), one sampling SOP for each

	product, or a combination of them. Clearly defined and documented procedures have to be available. They should take into account requirements of 7.33. Sampling plans for raw materials, intermediates and APIs have to be available. • <u>Testing</u> Analytical methods and test procedures should be cross referenced (e.g. pharmacopoeia) or described in such detail that analysts with the usual knowledge and expertise are able to understand how to proceed. It is recommended to include the necessary formulas (such as one including all the factors with explanation of each one, and another simplified) to carry out any calculation needed, and to make easy the review by a second person. • <u>Approval or rejection of result (see also section 11.15) :</u> – Before approving and rejection of materials the criteria to be used, the results to be averaged should be specified in SOP(s). – The SOP(s) should describe the criteria for averaging and/or rounding results, comparing results against specifications and approving or rejecting results. – Control charts can be used in detecting trends and atypical results which may require additional evaluation (for useful documentation see Institute of Validation Technology, http://www.ivthome.com) – Rounding results should be performed according to pharmacopoeia or other recognised system (see also revised ICH Guideline Q3A). – Care should be taken when averaging results involving atypical values (e.g. outliers) or when single values are out of the specification limit. • <u>Recording and storage of laboratory data</u> The content of the SOP(s) has to be in accordance with requirements of 6.6, and should describe what data should be recorded and reported, and where and how long this data should be retained. The responsibility for the integrity of retained records and relevant raw data should be assigned. See 6.13 when establishing retention times. When managing electronic data, systems should be appropriately validated (see the current GAMP Guide for Validation of Automated Systems in Pharmaceutical Manufacture for reference and http://www.labcompliance.com)
11.12	In order to check the specifications, sampling plans and test procedures for raw materials and intermediates, only selected parameters need to be tested. Sometimes one test method can provide enough information (e.g. an HPLC method may be at the same time an identification, purity and impurity method). The detection and quantification limits and precision of the methods used should be in accordance with the specification levels. The Quality Unit is responsible for reviewing and approving sampling procedures, but sampling may be carried out by people from other departments provided they have been appropriately trained. When appropriate there can be “in-house” specifications in addition to those in the registration/filing.
11.13	When establishing API specifications the following guidelines/documents should be taken into account: – ICH Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.

	– ICH Q6B: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological / Biological products – ICH Q3A: Impurities Testing Guideline: Impurities in New Drug Substances. – ICH Q3C: Impurities: Residual Solvents – Ph. Eur. Technical Guide for the Elaboration of Monographs – Dec. 1999 Once historical data have been collected, the established specification limits may be based on process capability, wider ranges should be justified (for example complying with ICH guideline for residual solvents). Justification for tightening specifications unless there is a therapeutic or safety justification should be retained.
11.14	The QC laboratory should use laboratory notebooks (bound notebook pre-numbered) or an equivalent laboratory notebook (one option is the use of loose sheets pre-numbered, the printing have to be controlled and also the storage as control records, another option is an electronic data collection system) to record the raw data at the time they are produced.
11.15	For product manufactured for the US market specific legal requirements (e.g. Barr Judgement, FDA “Guide to Inspection of Pharmaceutical Quality Control Laboratories”) are to be followed. The written procedure describing clearly what to do when an OOS is obtained should follow good scientific practice: – Checklist of potential defects in laboratory (e.g. calculations, methods, visual appearance, test procedure modified, experience of analyst during test, calibration of equipment...) – Similar checklist for potential deviations in production units – Check sampling and sampling devices – Guidance on when re-sampling (including whether an alternative sampling plan is appropriate) and re-testing might be carried out. Justification for these actions should be documented – Inclusion of a known control sample in any retesting – A valid OOS result should result in production investigations.
11.16	“Use by” dates are appropriate for those analytical reagents and standard solutions where its purity or standardised value can potentially change with the time. When appropriate, standard solutions can be re-standardised again and assigned a new “use by” date. The basis for the definition of the “use by” dates usually is experience of the laboratory and data from the supplier.
11.17	A SOP describing the policy of the company related to standards (both primary and secondary) use, records, obtaining, identification and storage should be in operation. When methods described in an official pharmacopoeia ask for reference standards, those have to be acquired from this pharmacopoeia. The routine use of a secondary standard tested against the primary standard is recommended.
11.18	For non compendial APIs, in house standards or those obtained from other sources may be used. Accepting a standard may require different tests than those applied to the regular product in order to confirm its suitability (purity determination by absolute methods, not applied currently in process testing), however some routine tests may be omitted. When a standard is used as a reference point for assays the mean and stan-

	dard deviation of the assigned assay value should be known. The method for obtaining and testing an in house primary standard should be described in writing. The purity may be assigned through a specific test for purity or by assigning a purity of 100 % taking away all the impurities (including water) determined by validated methods. Records of the tests carried out to identify and determine the purity should be maintained. A retest/expiration date should be assigned to the standard. It may need to be re-qualified. A formal certification of standards is needed when these are sent outside the control of the manufacturer.
11.19	The method of obtaining and testing secondary standards should be described in writing. The purity of those should be known. If used in assay determination the purity should be assigned testing it against the primary standard. A retest/expiration date should be assigned. A formal certification of standards is needed when these are sent outside the control of the manufacturer

11.2 Testing of Intermediates and APIs

11.20	Determine accurately “appropriate laboratory tests”, it does not mean “a lot of laboratory tests”.
11.21	Guidance for defining impurity profile(s) is provided in ICH Q3a and Q3c.
11.22	A practical approach of “appropriate interval” may be in the product regular quality review. The impurity profile could be useful for evaluating the impact on the product of critical deviations or major process changes.
11.23	See and follow ICH Q6A and ICH Q6B to determine if a defined microbial quality is necessary. Not every API needs to have specific microbiological specifications.

11.3 Validation of Analytical Procedures

see Section 12

11.4 Certificates of Analysis

11.40	Authentic: true, accurate record of results obtained, signed (also electronically) by authorised person (from Q-Unit) and dated.
11.41	Request for Certificate of Analysis may require the date of manufacture (final purification leading to API). Retest dates are normally calculated from date of release, should the date of release be well beyond the date of manufacture appropriate allowances in retest date should be made.

11.42	Include the acceptance limits in the certificate of analysis. When introducing numerical results, have in mind that limit test allow only to state "less than" value of the standard. Also consider non-numerical results. Certificates of Analysis for blended batches should be based on the results of sampling and testing the blend and not just taken from one of the components.
11.43	The certificate of analysis should allow traceability to the manufacturer and the way to contact the organisation that issues it.
11.44	It is not allowed to repackers/reprocessors, agents and brokers make a copy of the data reported by the original manufacturer eliminating the reference to it.

11.5 Stability Monitoring of APIs

11.50	Results of on-going stability program have to be evaluated at least in the product quality reviews. The following documents may be used as guidance: – ICH Q1A: Stability Testing Guidelines: Stability Testing of New Drug Substances and Products. – ICH Q1B: Photostability Testing of New Active Substances and medicinal Products. – ICH Q1D: Matrixing and Bracketing Designs for Stability Testing of Drug Substances and Drug Products – ICH Q1E – ICH Q1F CPMP/QWP/122/02: Guideline on Stability testing: Stability testing of existing active substances and related finished products.
11.51	Follow the requirements of Section 12.8 for validation of test procedures used in stability testing. Demonstrate that a method is stability indicating by stressing the API (temperature, humidity, ...) to achieve a significant degradation and determination of the purity and impurities: when purity decreases, new impurities should appear and/or existing impurities should grow. For products known to be stable from scientific point of view no stability testing required (e.g. inorganic salts).
11.52	If appropriate, store different bags of different batches of the same API into the same small-scale drums. Representative qualities and packaging configurations may be used to confirm expiry and retest dates for a range of equivalent products (see ICH Q1D, Matrixing and Bracketing).
11.53	First commercial production batches should normally be placed on the stability program. However, an example where 3 additional batches are not necessary is when the commercial batches are produced in the same equipment using the same process as that previously used in development. Fewer batches may also be taken if previous data (it may be data from pilot scale batches or from other site batches obtained by the same process) show that the API is stable for at least 2 years. This offers a reduction in current practice.

11.54	It is very important to remark that the guideline allows testing “at least annually” for batches introduced in the stability program after the first commercial production batches. When stability of API is beyond two years the annual batch needs only be tested at 0, 12, 24, 36... months. Based on scientific judgement, major changes or critical deviations may require additional batches to be placed on stability and / or more frequent testing.
11.55	Be careful with APIs with short shelf lives, point 11.54 is not applicable, and as a consequence the testing frequency will increase.
11.56	–

11.6 Expiry and Retest Dating

11.60	The supporting stability information on intermediates is not necessary to be obtained through stability studies complying with the ICH requirements for APIs. It may be obtained from published data or from a simple study based on test results of materials stored for some time.
11.61	The use of a retest date is recommended, this will allow using the API after this date, provided it complies specifications. See definition of Retest date.
11.62	To carry out stability tests following ICH guidelines on pilot scale batches is recommended, the data obtained (provided that commercial manufacturing scale employs the same manufacturing method and procedures and the quality of the API is equivalent) may be used to establish a preliminary retest period. When stability data from first commercial manufacturing batches are being obtained, this preliminary retest period can be extended if they allow it. Content of 11.52 also applies.
11.63	When performing a retest, the sample should be taken again from the containers where the API is, and should be representative of all the remainder of the batch. Retention samples should not be used.

11.7 Reserve/Retention Samples

11.70	Reserve/retention samples should be different from stability samples. It is not necessary that conditions of packaging and storing of reserve samples are equivalent to those of the stability samples. Storage containers and conditions should attempt as far as possible preserve the original quality and should be no worse than claimed storage conditions.
11.71	To avoid having different retention times for reserve samples for each product and each batch manufactured, it may be workable for companies to define a unique retention time for all batches and products of 3 years after the expiry or retest date (provided that there will not be distributed any batch or portion of a batch after its retest date). The retention times are minimum and provided these are met, reserve samples may be disposed of later than the minimum times.
11.72	–

Chapter 12 Validation

12.1 Validation Policy

12.10	Overall Policy The company should document clear and unambiguous policy related to all validation activities. Qualification activities are considered to be an integral part of validation. The policy should clearly show a companies rationale towards validation and detail how it will approach each key activity. Responsible Person Detail on responsibility during validation should be documented to ensure that commitment is made at the appropriate level.
12.11	Critical Parameters/Attributes A risk assessment should be performed to map out critical parameter attributes prior to validation. These parameters need careful consideration as they will form the basis for assessing the system to be validated. Ranges used for each critical parameter should be well defined and supported by development data and or historical data. The parameters, if not adequately controlled, could affect the critical quality attributes of the product. Further details on critical parameters can be found in ISPE guideline "Qualification and Commissioning".
12.12	Validation should extend to those operations deemed to be critical. Protocols used in validation should encompass those operations deemed to be critical. Non-critical operations need not form part of the validation study, for example material transfer in closed systems. Manufacturers should refrain from thinking they have to validate all operations. Validation of only critical operations will prove to be more cost effective and is scientifically sound.

12.2 Validation Documentation

12.20	Review and Approval Review and approval of protocols needs to come from personnel who are competent and have the authority to support the validation.
12.21	Acceptance Criteria Acceptance criteria are established in validation protocols in order to allow the measurement of success or failure of a particular validation. Acceptance criteria should be identified from previous experience and need to reflect the key parameters that are measured during validation. For example, for process validation levels of impurities need to be controlled in line with any registered specification. Meeting the limits for these impurities consistently would be a key acceptance criteria.
12.22	Deviations Observed Deviations during validation should be fully explained in the validation report.

	Conclusions and corrective actions need to be described. Significant deviations that impact product quality or reject batches that fail specification should be fully explained in the validation report. When API quality is jeopardised the validation should be evaluated as to whether it is best to stop the validation or amend the protocol to manufacture additional batches. Careful consideration is required before this decision is made as the underlying reason for the failure should be fully understood and acted on.
12.23	-

12.3 Qualification

12.30	For full comment on Qualification see ISPE Baseline Guide on "Qualification and Commissioning". • Design qualification is documented evidence that : – user requirements document has been established by production and technical/maintenance services. – technical propositions made by engineering department have been approved by concerned units as production, technical/maintenance services, quality control, quality assurance units in terms of equipment design and automatic operation design. • Documented evidence should consist in formal approval of: – meeting minutes – facility layouts – PID – Supplier detailed layout • Design qualification should apply to (in terms of equipment and/or automatic operation) : – new process – new step in actual process – modification of an equipment in a process

12.4 Approaches to Process Validation

12.40	Process Validation The purpose of process validation is to demonstrate that a particular process can perform effectively in a robust and consistent manner to produce material that meets predetermined specifications and quality attributes.
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12.42	–
12.43	Concurrent validation Concurrent validation is a particular form of prospective validation, in which the batch or batches produced are released, based on more extensive testing, before the entire validation study is complete.

12.44	–
12.45	Retrospective Validation Retrospective validation requires a protocol that covers in detail the acceptance criteria and batch information that will form the basis for validation. Batches that fail to meet specification or are out of trend needs to be discussed. The number of batches chosen should be statistically based. Guidance on the number of batches chosen can be found in United States vs. Barr Laboratories [812 F.Supp. 458, 474-475, 477 (D.N.J. 1993)]. The "general rule" from the above judgement is that between 20-30 batches is required, but a firm can depart from this number provided it can support any such departure with statistical or other evidence that supports validation.

12.5 Process Validation Program

12.50	–
12.51	–
12.52	–

12.6 Periodic Review of Validated Systems

12.60	Revalidation Product Quality Reviews (see 2.5) should assess the requirement for revalidation. Significant changes made to systems/processes or significant changes in product quality (see chapter 13) will require evaluation for revalidation.

12.7 Cleaning Validation

12.70 –	See APIC guide on cleaning validation for full comment
12.76	(http://apic.cefic.org/framecommunica.html).

12.8 Validation of Analytical Methods

12.80, 12.81	Analytical methods used directly from recognised standard references (e.g. Pharmacopoeia) need only to be demonstrated suitable for use. System suitability tests can be found in European Pharmacopoeia. If modified pharmacopoeia methods or in-house methods (non-pharmacopoeia) are applied for compendia APIs equivalence with the relevant pharmacopoeia method has to be demonstrated and a report has to be made available on request. The level of the validation required for in-process controls should be evaluated depending on the influence on the final API quality. Guidance on the levels of analytical method validation can be found in ICH Q2a and Q2b.
12.82	Appropriate qualification Qualification can be performed in house or provided by the equipment supplier. If supplier qualification information is used it should be approved by the Quality

	Unit as suitable for its intended use.
12.83	Modification needs to be covered by a change control system.

Chapter 13 Change Control

13.10	–
13.11	Having defined the quality of an intermediate or API, usually in terms of a specification, it is essential to maintain this quality, as there is interrelationship between "quality" and the two other essential properties of an API, "safety and efficacy", ANY change which may affect the quality of the intermediate or API may also change the safety and efficacy. It is thus essential that all changes are evaluated before being introduced. It is intended that not only changes to the way of producing or analysing the product should be covered by the Change Control System, (CCS), but this should also cover other changes to for examples buildings and equipment, utilities, suppliers of starting materials, etc. Changes in any part of the quality system should not be confused with "deviations" and the ICH EWG made it clear that the procedure for dealing with deviation, (as described in § 2.17 and § 8.15 as well as §.6.72) is not the same as that to be used for changes. The diagrams below makes the difference between "a change" and "a deviation" apparent. NOT PLANNED == DEVIATION <u>was not planned</u> and now has already occurred ↑ EVENT ↓ PLANNED == CHANGE <u>is planned to occur</u> i.e. the event has not occurred yet; but there is however the intention to <u>do something different in the future.</u> ↘ As preparation for a possible Change TRIALS are often initiated. TRIAL is defined as something that is planned for a limited time.

However as "Trials" are not mentioned anywhere in the ICH Guide, it will be advisable to handle them under the CCS however the approval process to conduct a "Trial" should be very simple. Precautions should be taken to prevent "Trial material" leaving the premises, or other being used without authorisation. It is recommended to include the description of the trial procedure in the CCS SOP.

Although in very small companies, not operating under a Quality System, "Changes" may have been agreed verbally between staff involved, the word "formal" indicates that the way in which the CCS needs to be laid down in writing and approved by appropriate persons including (according to § 2.22 – 6) someone from the quality unit.

It would be acceptable to have more than one CCS in a company and there might be several "formal" CCSs covering marketing-relevant changes, quality-relevant changes, engineering changes, process changes etc. The essential element is however that the proposed changes are written and approved.

If there is even a slight possibility that the proposed change could cause the production or control to be different, then this proposed change should be evaluated before being initiated. Thus it is incorrect only to deal with changes that definitely will have an effect using the CCS.

Although theoretical only changes which could affect "productions and control" need to be handles under the CCS, nevertheless the ICH EWG intended that any changes which affect the "manufacture" (i.e. not only production and control, but also packaging, labelling and storage etc) should be handles by the CCS.

13.12	There are four key words which should govern how the CCS is run: <u>Propose</u>, <u>Review</u>, <u>Evaluate</u> and <u>Approve</u>. These are shown in the following flowsheet <table border="1"> <thead> <tr> <th data-bbox="384 376 858 412"><u>Activity in the Change Process</u></th><th data-bbox="858 376 1286 412"><u>Relevant ICH Paragraph</u></th></tr> </thead> <tbody> <tr> <td data-bbox="384 412 858 555">Possibly review of the proposed change with affected dosage form manufacturers and/or customers, where appropriate</td><td data-bbox="858 412 1286 555">§ 13.17</td></tr> <tr> <td data-bbox="384 555 858 591">Propose a Change in writing</td><td data-bbox="858 555 1286 591"></td></tr> <tr> <td data-bbox="384 591 858 627" style="text-align: center;">↓</td><td data-bbox="858 591 1286 627"></td></tr> <tr> <td data-bbox="384 627 858 1254">Forward this Proposal to those units in the organisation who are best able to pass judgement by reviewing the implications on the proposal, one of which should be the responsible Quality Unit. (Other typical units could be the stability testing unit, development department, purchasing, production, costing etc). The Regulatory Affairs unit generally would also be asked to judge whether and where the change, if internally approved, might need external approval and/or requires customer notification. Usually the SOP governing Changes will specify within what time frame an answer should be given.</td><td data-bbox="858 627 1286 1254"> § 13.12 § 13.13 § 13.16 § 1.1 (Last paragraph) </td></tr> <tr> <td data-bbox="384 1254 858 1361">Have lists of the documents which will be affected by the Change prepared.</td><td data-bbox="858 1254 1286 1361">§ 13.14</td></tr> <tr> <td data-bbox="384 1361 858 1397" style="text-align: center;">↓</td><td data-bbox="858 1361 1286 1397"></td></tr> <tr> <td data-bbox="384 1397 858 1541">Review and summarise the answers and prepare the Approval (or Rejection) statement, and have this signed.</td><td data-bbox="858 1397 1286 1541">§ 13.13</td></tr> <tr> <td data-bbox="384 1541 858 1576" style="text-align: center;">↓</td><td data-bbox="858 1541 1286 1576"></td></tr> <tr> <td data-bbox="384 1576 858 1787">Request an evaluation of the success (or otherwise) of the change. This should be prepared by the originator of the original proposal and reviewed and approved by the Quality unit</td><td data-bbox="858 1576 1286 1787">§ 13.15</td></tr> </tbody> </table>	<u>Activity in the Change Process</u>	<u>Relevant ICH Paragraph</u>	Possibly review of the proposed change with affected dosage form manufacturers and/or customers, where appropriate	§ 13.17	Propose a Change in writing		↓		Forward this Proposal to those units in the organisation who are best able to pass judgement by reviewing the implications on the proposal, one of which should be the responsible Quality Unit. (Other typical units could be the stability testing unit , development department, purchasing, production, costing etc). The Regulatory Affairs unit generally would also be asked to judge whether and where the change, if internally approved , might need external approval and/or requires customer notification. Usually the SOP governing Changes will specify within what time frame an answer should be given.	§ 13.12 § 13.13 § 13.16 § 1.1 (Last paragraph)	Have lists of the documents which will be affected by the Change prepared.	§ 13.14	↓		Review and summarise the answers and prepare the Approval (or Rejection) statement , and have this signed.	§ 13.13	↓		Request an evaluation of the success (or otherwise) of the change. This should be prepared by the originator of the original proposal and reviewed and approved by the Quality unit	§ 13.15
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	By using the word proposal it is clear that an application, detailing what it is proposed to change, is necessary. It is recommended that this should not only cover the proposed change itself but should give some proof not only that the change will work (by having run “trials”), but also an indication of the cost of the change (i.e. the cost of generating new stability data). Some unit should draw up a list of customers who could be effected by the proposal. The fact that the words reviewed and approval are used twice indicates that the initial review and approval by the appropriate organisational unit needs to be followed by the review and approval by the QU(s) (a task assigned under § 2.22-9). This is particularly essential where the QU(s) may not have sufficient expertise to fully evaluate the implications of a proposed change, e.g. on the Marketing Approval, / DMF / API use. In a similar vein it would be appropriate to review proposed changes to facilities, support systems (e.g. water treatment systems), or computers by persons with appropriate expertise who are independent of the person or group applying for the change.
13.13	The wording indicates that although a classification procedure may help such a classification procedure was not a requirement of a CCS. By using the words Scientific judgement it is made clear that it is impossible in such a guide to prescribe exactly how each type of change should be dealt with. Thus the justification for approving a proposed change should not slavishly follow a prescription, but each case should be judged on its merits. Although theoretically : there is no specific requirement to put the reasoning (justification) for approving (or rejecting) a proposed change in writing, companies are strongly advised to provide a written justification, (even if only in a few lines): This could for example include the reasoning why the proposed change is being approved, and why (or why not) a revalidation of the production process or analytical method is (or is not) necessary.
13.14	The text makes it clear that solely approving a change is insufficient, but there also needs to be a programme which identifies what needs to be done so that the approved change may be carried out. The critical words here are to ensure that documents affected by the changes are revised, The principle raised here is that of checking that the documents (e.g. DMF, other Regulatory documents, in-house instructions, and procedures, information given to customers, etc) which might be affected were actually revised. The EWG purposely gave is no advice on how this should be done, and thus each company is free to devise its own procedure for meeting this requirement. A possible way would be to require that the originator and each organisational unit which reviews or approves the proposed change list the document in their areas or responsibility which will need to be changed and add this list to their “Review and Approval” document. After approval each organisation unit is then responsible for carrying out the change to the documents and reporting the successful completion. This is however not the only way of ensuring that the requirements of this paragraph are met.

13.15	The intention of this Sub-section is that there should be a review of the effect of the introduced change upon the products effected, be it by a process change, be it by a change in the testing procedure, or be due to changes in other factors which may affect the quality of the products. As this is an activity, it should be recorded that such a review has taken place, and the conclusions drawn should also be recorded. (See also the Key Words in § 13.16 and §13.17).
13.16	In the ICH Expert Working Group it was accepted that there would be a large number of compounds, in particular inorganics which would still exhibit the same stability profile, even if the process had been considerable changes. Thus there is no need always to add samples from the modified process to the stability monitoring programme. This paragraph not only applies when there are "process" changes, but other changes too, (such as the improvement to an analytical method resulting in the detection of a previously unknown breakdown product) could also affect the retest or expiry date and thus this paragraph was widened to include all critical changes, and this needs to be considered. This paragraph is only applicable when there are critical changes (and as "critical" has now been clearly defined, (See the Glossary in the ICH Q7a document GMP for APIs). Thus not every change which will be reviewed under the CCS will fall into this category. Being in mind the definition of "critical" it is essential to remember that if the predetermined limits are not held, particularly if they are revised, and this results in the API not meeting its specification then these limits are critical. Under these circumstances the potential effect upon the stability should be very carefully evaluated. It is expected that the "evaluation" should be recorded, as should the conclusions as to whether additional stability testing is necessary. This record should obviously contain some scientific justification for the decision taken, This may take the form of a short statement, (e.g. "the original compound is stable for over 4 weeks at 80°C and thus the increase in the drying temperature to 65°C is unlikely to cause additional product breakdown, and no increase in the known or unknown impurities was detected") for it is not expected, nor should it be required that such scientific justification will require a full written discussion of what might possibly occur.
13.17	It is not necessary to inform every dosage form manufacturer who has ever bought the product about the change,. If there has been no supply of the product to a dosage form manufacturer over a longer period of time, the exchange of information should be re-evaluated (unless such information flow was part of the any original agreement with such users). Emphasis is placed on "procedures" (as it is assumed that if specification limits were changed the authorities would need to approve this, but may not even need to be informed about changes to "procedures"). The selection criteria is that the change can impact upon the quality of the API. Under such circumstances current users should be informed. The words "impact the quality" should not be confused with "meeting the specification". Only too frequently in the past have dosage form manufacturers discovered that although the purchased API met the pharmacopoeia or other agreed specification, nevertheless its' behaviour during subsequent processing to a dosage form was quite different. This is because there are still too many physical characteristics of an API

	which cannot easily be routinely measured. Under these circumstances, if the change is in the final step of the API manufacture and involves a change of equipment, solvent, isolation or purification conditions, it is advisable to contact key customers before introducing the change and provide demonstration ("Trial") material for experimental use. In this way the API manufacturer not only avoids the potential loss of a customer, but also the need to reverse an already approved change.

Chapter 14 Rejection and Reuse of Materials

14.1 Rejection

This is an entirely new chapter in a GMP guide, introduced because the concepts explained therein were necessary to avoid having auditors or government inspectors treating the reworking (or reprocessing) of APIs in the same way as the reworking (or reprocessing) of medicinal products were being treated.

There is an essential difference between the reworking (or reprocessing) of a chemical such as an intermediate or an API and the reworking (or reprocessing) of a physical mixture such as a medicinal (or drug) product. In the case of chemicals the techniques of reprocessing or reworking have been used for centuries now to purify substances and remove impurities, whilst the reprocessing (or reworking) of a medicinal (drug) product rarely results in a purer product and may even result in a product with a shorter shelf life or lower bio-availability.

14.10	The intention of the wording is that this section applies only when there is an "established specification" for an intermediate, i.e. the section should not be applied when the intermediates is "monitored" to ensure that the use criteria for the next step (e.g. less than 0.5% free ketone) are met, (because in such cases the process step may be continued for a length of time till the use criteria are met). Similarly the paragraph can only be applied to intermediates which are sufficiently long-lived that they can be held until the tests have been completed, even if such intermediates have not been isolated. When material has actually been found not to meet specification simply retaining this material in quarantine is insufficient (except for material being under OOS investigation), but it specifically needs to be identified (i.e. physical or in the computer stock lists) as "DOES NOT MEET SPECIFICATION". Some companies actually place a red "Rejected" label on the containers, but in such cases there should be an SOP which indicates that a "Rejected" label does not automatically mean that the material has to be "Destroyed". The second precaution is to quarantine the materials. This may be done by giving the material a special symbol in the Material Management computer to indicate that it is not in Quarantine awaiting test, but has already been tested and found deficient. Where such a system is not available, then simple management tools, such as stock cards, and even the containers themselves, need to be marked so that it is seen that the material is "On Hold" (and some companies use this term to denote such a quarantine status. The statement "can be reworked or reprocessed" replaced the requirement that such material should be "rejected" during the discussions in the WG to indicate quite clearly that, in the cases of intermediates and APIs, further processing is one option of treating materials not meeting specification. Nevertheless the input specification of

	the material has to be met. One possibility which was not specifically mentioned, is that of actually using the batch of rejected material in the process without reworking or reprocessing it. § 2.15 might be so interpreted to mean that intermediates which do not meet specification can still be released under quarantine for use in the next process step, and the "completion of the evaluation" can be carried out at the end of the process, i.e. a check is made whether the detected deviation from specification has no effect upon the final product. If such a procedure is permitted by the company's SOPs then there should be the requirement that such a step be classified as a "Concurrent Validation" step, because it will rarely have been covered by the normal prospective validation activities. As there is no definition of "Rejected" in the Guide it is left to each company to lay down its' own policy on this topic in writing. A reasonable policy would usually state that if materials are truly "rejected" i.e. cannot be treated in any other way, apart from permanent disposal, then a record should be maintained of when and how this disposal was carried out. This procedure should also cover API starting materials which are returned to the supplier as being unsuitable for use, such returns however should be accompanied by the provision that the supplier should not just blend the "returned" material with good batches and then resubmit this.

14.2 Reprocessing

14.20	The word Reprocessing was originally chosen by the CEFIC / EFPIA Working group to indicate that one was dealing with a Repeat of a PROCESS step which had already been carried out. In spite of the considerable rewording that went on after the publication of the CEFIC /EFPIA guide, this concept has been retained. Thus the essential element of REPROCESSING is that it is not a deviation from an existingly-decribed process but is solely a repeat of this. One might therefore argue that reprocessing is thus automatically covered by the original process description, (although most companies do still mention in their process descriptions from which steps "reprocessing" may be initiated. The § 14.10 covers the situation where material does not conform to established specifications whilst in this paragraph the concept is widened to also permit reprocessing of material even if it originally met the established specifications. This later situation could arise when remainders of a batch (often called "tailings") are not packed into a partially filled drum, but are returned to the process and are either blended with the next, or subsequent batches, or are even re-dissolved and re-crystallised out. If reprocess had only been permitted for defective material, such reprocessing of "tailings" (as they came from acceptable batches) would not have been permitted. The very essence of this section is found in the words "repeating a step or steps that are part of the established manufacturing process is generally considered acceptable". This positive statement thus indicates to auditors and even governmental inspectors that (possibly in contrast to medicinal products) repeating one or more steps from the already established process was not objectionable. The examples given are only examples of typical reprocessing steps and reprocessing is NOT limited solely to these examples. It is important to remember that regular reprocessing of materials is often an indica-

	tion of a process not running "under control". Certainly when the majority of the batches produced within a specific time frame need to be reprocessed, this is a clear indication of the inadequacy of the original process. The Barr judgement on the interpretation of GMP as applied to solid dosage forms of medicinal products (e.g. tablets) and given in a court case in the USA in February 1993, even went so far as to state that if more than 10% of tablet batches needed to be reprocessed then the process was considered no longer validated, but the EWG did not accept this principle for intermediates or APIs due to the much greater variability in the factors which might make reprocessing necessary, e.g. APIs from materials of natural origin. The examples given are only examples of typical reprocessing steps and reprocessing is NOT limited solely to these examples.
14.21	–
14.22	The examples given in these two paragraphs were added to give additional guidance to those persons unfamiliar with the concepts of "reprocessing".

14.3 Reworking

14.30	The definition of "rework" should be fully understood before any decision to "rework" a batch is taken. This is because reworking involves another process which may not be covered by the original process description. Thus in many countries "reworked material" may not be used commercially until approval of the authorities has been obtained. The only exception to this rule would be if "alternative processes" had been approved and it was clear that material originally made by the one process could be "reworked" using the alternative and approved process. The important part of this section is the requirement that NO reworking should be initiated before the reason for the non-compliance has been determined (i.e. the "investigation" should have been completed).
14.31	–
14.32	The detail given in these two sections again indicates that if material is "reworked" a much deeper assessment should be made of the resulting product and the advice that Concurrent validation is a suitable means of dealing with "reworking" only underlines the fact that it would be insufficient solely to check the reworked material against the original specification, due to the possibility of that reworked material may contain new impurities or may have different physical properties such as crystal structure. This is very rarely the case with reprocessed material and thus this § 14.31 gives advice which is specifically appropriate for reworked material.

14.4 Recovery of Materials and Solvents

14.40	Recovered materials DO NOT have to meet the same specification as the original materials, and although in most cases the specifications will be laxer than for original product, this may not always be "appropriate", and a tighter specification may be necessary to prevent difficult to remove impurities being enriched through the process. Although the examples of "recovery" only include process steps which arise from the original process, nevertheless it is acceptable to recover APIs themselves, irrespective of their physical form, e.g. recovery from a medicinal product itself.

14.41	Specific approval is also given for recovering solvents, which not only makes economic sense, but is environmentally more friendly. Again there is NO REQUIREMENT that recovered solvents need to meet the same specification as the original materials, and although in most case the specifications will be laxer than for original product, this may not always be "appropriate", and a tighter specification may be necessary to prevent difficult to remove impurities being enriched through the process.
14.42	The important words in this paragraph are "adequate testing". How adequate the testing needs to be will depend on the projected use of the recovered material. Recovered solvents only being reused in the same process, i.e. being recycled, will need less testing than those being recovered and then possibly being used in totally different processes. In the former case it might be adequate to solely check refractive indices or specific gravity's and maintain these within an accepted range whilst in the later case it may even be necessary to quarantine the recovered solvent until a whole batch of chromatographic or other tests have been completed. There is however no specific requirement that ALL recovered solvents need to be quarantined before reuse. The criteria of "suitability" does not necessarily mean meeting the original specification, (as is discussed in § 14.41 above).
14.43	The documentation required here can, in most cases, only be of a general nature, unless the quantity of recovered solvents per batch can be measured. This is very rarely the case when solvents are continuously recovered in a campaign or in continuous production. In such cases it may only be possible to record how much new solvent is being added in what period of time to make up for losses caused by the recovery process. It is not expected that records more detailed than those required to for economic purposes such as a record of the overall use of materials should be retained. However the record should indicate whether the solvent had been recovered from the same or from a different process, to help in identifying unknown impurities if these start increasing during the production campaign.

14.5 Returns

It is important to realise that this Section equally applies to Agents, Brokers, Traders, Repackers and Relabelers, as stated in § 17.80. As companies who physically treat APIs, e.g. micronizers, or granulators will automatically have to Repack" the product after such treatment this section applies to such companies also.	
14.50	When material has been returned, simply transferring this material in quarantine is insufficient, but it specifically needs to be labelled (i.e. physical or in the computer stock lists) as "RETURNED". Some companies actually place a prominent "RETURN" label on the containers but care needs to be taken which would later be replaced with the label indicating the decision taken, e.g. "RELEASED for REPROCESSING" or "RETURN to ORIGINAL MANUFACTURER". The second precaution is to quarantine the materials. This may be done by giving the material a special symbol in the Material Management computer to indicate that it is not in Quarantine awaiting test, but has already been tested and later returned. Where such a system is not available, then simple management tools, such as stock cards, and even the containers themselves, need to be marked so that it is seen that the material is "On Hold" (and some companies use this term to denote such a quarantine status).

14.51	The difficult is knowing under what conditions the returned material has been shipped or stored. Although in some cases, where the material is known to be very stable, (e.g. stable after 6 months continuous storage at 40°C) there may be little doubt as to the quality in many cases these doubts will be present. This means therefore that such material SHOULD NOT be returned to the market. As this Section also applies to Agents, Brokers, Traders, Repackers and Relabelers who very rarely will be in the position to reprocess or rework material they will need to return it to the original manufacturer for such steps to be carried out. It is thus ESSENTIAL that Agents, Brokers, Traders, Repackers and Relabelers have a good traceability system, (as required by § 17.20) that they can determine who was the original manufacturer of the returned material.
14.52	The "use or disposal" of the returned material will obviously include whether it was reprocessed, reworked (or even "recovered") and which batch number the reprocessed, reworked (or even "recovered") material was given after the reprocessing, reworking (or even "recovery"). Such batches will then need new processing, packaging, labelling and distribution records as required for example by §6.5, § 6.6, § 9.4, § 10.2 etc.

Chapter 15 Complaints and Recalls

The concept of recall in its original meaning does not really apply to API manufacturers as they are never able to recall the finished dosage form from pharmacies, hospitals, distributors etc. This is the task of the finished dosage form manufacturers. Even notifying local and national health Authorities in case of life threatening situations can only be made in tight cooperation with the finished dosage form manufacturers, as they are the ones who distribute the finished dosage form to the market.

In the event that the release status of a distributed API can be questioned the API manufacturer should be able to trace all parts of the batch in question which may have been distributed to customers (finished dosage form manufacturers, agents, distributors, etc.) or what may still be on storage.

The API manufacturer should have a procedure describing the process and responsibilities related to recalls/product (API) traceability, and should be able to document that batches can be traced and reconciled. Key personnel involved should be identified. Likewise, the responsibility for notifying customers and local authorities, if applicable, should be addressed.

Chapter 16 Contract Manufacturers, including laboratories

Although the word "manufacture" was defined in the ICH Q7a GMP Guide to mean "all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage, and distribution of APIs and related controls", nevertheless the words "and laboratories" were added to the title of this chapter to make it perfectly clear that this chapter also applies to any laboratory which might carry out any analysis for the API manufacturer according to a specific request or agreement. There was the wish to specifically include "Contract Micronisers" in the title, but as "manufacture" includes <u>any</u> production step then contract micronising is thus automatically included in the application of this chapter.	
16.10	The contractor should take specific measures to prevent cross contamination, such as validating the cleaning procedures, using dedicated facilities where necessary, etc. Maintaining traceability should include knowing what materials were received, and when, how and where were they processed, and when were they packed, labelled and stored.
16.11	The EWG of ICH Q7a chose the word "evaluation" (rather than "audit") to indicate that it would <u>not always</u> be necessary to physically audit the potential contract manufacturer if there was sufficient knowledge available to ensure that the contract acceptor would be in compliance with GMP. If however the work being given out under contract included "critical process steps" and the potential contractor possibly had little experience of GMP then a site audit by a person(or persons) experienced in API GMPs would be highly recommended. It is worth pointing out that serious consideration should be given to <u>audit</u> laboratories inexperienced in GMP, carrying out contract testing, In such cases guidance should be given to the contract laboratory (particularly in unequivocal record keeping) to ensure that the quality standard of the activities will be in compliance with the Q7a requirements.
16.12	Although it is very rare that work carried out under contract is not covered by a written contract, (which will usually cover the extent and cost of the work to be done) the important point that is very often neglected is a clear agreement between the parties as to who is to be responsible for the specific responsibilities of the Quality Unit. In particular who will carry out what analyses before and after any production work has been carried out, and who will actually release the material for further use, (including supplying to the market in the case of repackers, or contract micronizers etc.). Lines of communication between contract giver and contract acceptor should be included in the contract and this should include the names / positions of the contact partners.
16.13	As was pointed out in § 16.11 it may not always be necessary to physically audit the contract acceptor, however, as clearly stated here, the contract giver should always be <u>allowed by the contract</u> to audit if he so desires. This should be clearly agreed before any contract is signed, and should be a condition of signing.
16.14	Even if "sub-contracting" is not specifically mentioned in the contract under no circumstances should the contract acceptor pass on to any other company any of the work entrusted to him. Even passing on such work to another facilities located at a different site should be expressly forbidden as these could totally negate the "evaluation" which may have been carried out, unless this was actually approved by the contract giver.

16.15	The intention of this paragraph is to ensure that the ORIGINAL records of any manufacturing activity (including laboratory testing) should be retained by the contract acceptor (and one should not tear out pages from bound notebooks to give these to the contract giver). If the contract giver wishes to have records of activities carried out, COPIES of the original records should be supplied. Such copies are often specifically marked by the contract acceptor to indicate that these are copies. Such records should be stored at the contract acceptor at a minimum according to the guidance given in Q7a, § 6.13.
16.16	This statement is essentially already covered by the requirements of § 16.10, - complying with GMP - because this also means that the contract acceptor has to comply with Chapter 13 Change Control. However it is stated again here to make it clear to those companies who have had little experience of working under GMP that "changes ARE NOT PERMITTED" unless these have been approved by the contract giver. If however the contract includes wording such as "developing a process", including "adapting the test methods where appropriate" then the contract giver has specifically requested that changes should be made, and this paragraph would not be applicable. Under such circumstances it is the responsibility of the contract giver to ensure that material produced or tested under such a contract is only used when it meets any regulatory requirements.

Chapter 17 Agents, Brokers, Traders, Distributors, Repackers, and Relabellers

17.1 Applicability

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17.2 Traceability of Distributed APIs and Intermediates

17.20	This Section needs very little interpretation. The EWG of ICH Q 7a gave a very detailed listing of the documents which need to be retained in order to assure the traceability of any material passing through the hands of an Agent, Broker, Trader, Repacker, etc. Although the word "should" has been used in this section, nevertheless any Agent, Broker, Trader, Repacker, etc. who is not retaining the full list of these required documents would need to have comparable documentation which fulfils exactly the same purpose. It should be noted that the wording "retained and available" means not only retained and made available to the authorities but also to the customer of the Agent, Broker, Trader, Repacker, etc., on request. It is essential that the identity (i.e. name) and the address of the original manufacturer be given to the customer (see also § 17.61. If the Agent, Broker, Trader, Repacker, etc. does not know or cannot provide the name and address of the original manufacturer of the commercially available intermediate or API this would then be a serious violation of this GMP Guide. It is already known by many Brokers, Traders, Repackers, etc. that one should not ac-

	cept at face value certain names and addresses of companies provided by state controlled export agencies, as their practice of changing the source of the API depending on which state company has stocks available are well known. It should be pointed out that in the future in the EU, if a "Qualified Person" releases a Medicinal Product made from an API from an unknown manufacturer this would be a serious violation of his/her ethical duties as a "Qualified Person". The inclusion of the wording "authentic" Certificates of Analysis is to indicate that it is <u>not acceptable</u> to photocopy the Certificate of Analysis of the original manufacturer onto the letter heading of the Agent, Broker, Trader, etc.

17.3 Quality Management

17.4 Repackaging, Relabelling and Holding of APIs and Intermediates

17.5 Stability

No comments are foreseen for these parts as the text of the ICH Q7a document already is comprehensive enough.

17.6 Transfer of Information

17.60	This section is included to ensure that information which would normally be transferred by the API manufacturer to the dosage form manufacturer as required under § 13.17 is transferred instead to the Agent, Broker, Trader, Repacker, etc. The meaning of "all quality and regulatory information received from the API manufacturer" means much more than the information listed in § 17.20 and would of course cover any changes made by the manufacturer to the process, the specifications (specifically the deletion of a test parameter) the test methods or the retest date.
17.61	This is a unequivocal statement, specifically inserted in the ICH Q7a guide at the request of the dosage form manufacturers, and supported by the authorities. It makes it clear that the process of covering up the source of APIs, ("neutralising"), is no longer acceptable.
17.62	The authorities expect that Agents, Brokers, Traders, Repackers, etc. will not only comply with this guide but also actively cooperate with the authorities to clarify matters which only the Agents, Brokers, Traders, Repackers, etc. may be aware of. Thus when the authorities have reasons to involve Agents, Brokers, Traders, Repackers, etc. in their investigations, the later are obliged to respond to "a request" in a timely manner. Agents, Brokers, Traders, Repackers, etc. should therefore, in order to minimise any risks to patients, reply promptly and fully to such requests for information from the authorities.
17.63	If a request is made to an Agent, Broker, Trader, Repacker, etc. for a Certificate of Analysis <u>all the requirements</u> listed in § 11.4 (Certificates of Analysis) <u>must be met</u>. In particular the requirement that if NEW analyses have been carried out, (not only by a Repackers or Relabeler but also by a broker or agent as well), these should be given in a NEW Certificate of Analysis showing the name and address of the laboratory that carried out the NEW tests. It would <u>not</u> be acceptable to replace the original values certified by the original manufacturer by the new values from the re-testing laboratory but rather TWO separate Certificates of Analysis should be provided to the customers, the Certificate from the original manufacturer (with a translation when appropriate) and the second Certificate from the re-testing laboratory. If the re-testing laboratory takes over ANY TEST RESULTS from the original manufacturer into the NEW certificate, this should be clearly indicated for each test result taken over. (This is necessary to check, when necessary, where the raw data may be located - and thus audited - in order to confirm the authenticity of the certified results). It should be pointed out that if an Agent, Broker, Trader, Repacker, etc. involves a contract laboratory in any testing of any materials handled by them, the requirements of Chapter 16 (Contract Manufacturers including Laboratories) are to be followed.

Chapter 18 Specific Guidance for APIs Manufactured by Cell Culture/Fermentation

18.1 General

The explanations given to clarify the “how to do” of this chapter is given from the perspective of “classical fermentation's”	
18.10	No further explanation needed; note that “In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.”
18.11, 18.12	Definitions for “biotechnological processes” and “classical fermentation” are given, that cover differences between these two types of fermentation processes, e.g. regarding type of organisms used and products obtained.
18.13	This subchapter refers to the need to control bioburden, viral contamination and/or endotoxins during the fermentation and recovery steps. This need is more outspoken for products from biotechnical processes than for those from classical fermentation's, unless the API produced will be processed further to a sterile drug product. Additional guidance is given in later subchapters.
18.14	In some classical fermentation the start of a fermentation is not always by making use of a vial of the cell bank, but by using for the inoculation a part of a previous, successful fermentation
18.15	Fermentators need not always be placed in areas that are supplied with air of a controlled quality (Grade C, as defined in “The rules governing medicinal products in the European Community”). Areas of level I as defined in ISPE-guide Bulk Pharmaceutical Chemicals could be appropriate.
18.16	Parameters for controlling critical operating parameters during fermentation could be the following, but are not limited: temperature, oxygen concentration, pH, agitation rate, concentration of critical starting materials or Excipients etc. The level of protection of the intermediate or API is dependant on the nature or future use of the intermediate or API and could be seen in relation to the way the downstream processing is performed. Some API's have an inherent potential as antibacterials or preservatives. For classical fermentation's normal hygienic conditions should be in place, in that case there is no need to monitor bioburden and endotoxin levels.
18.17	–

18.2 Cell Bank Maintenance and Record Keeping

General remark: It is usual to maintain a Master Cell Bank (MCB) and a Working Cell Bank. By maintaining a MCB many production runs can be done with the same organism	
18.20	No further explanation needed, but as stated in 18.14, the use of a cell bank for a next fermentation is not always necessary.
18.21	–

18.22	–
18.23	For classical fermentation's it will often be difficult to establish the usage period of a cell strain before it is used, however cell banks can be monitored to determine suitability for use by recording the productivity (in a quantitative and qualitative way) of the organism.
18.24	–

18.3 Cell Culture/Fermentation

18.30	–
18.31	–
18.32	In case a company performs more than one fermentation process, precautions should be taken during handling of cell cultures that prevent contamination. Examples could be: dedicated inoculation areas, dedicated personnel or gowning and appropriate cleaning procedures for utensils.
18.33	–
18.34	No further explanation needed; see 18.42.
18.35	An additional reason for sterilising culture media could be the quantitative aspect of the fermentation.
18.36	Procedures that determine the impact of the foreign growth on the product quality can take into consideration the established experience a company may have with fermentation's that have shown foreign growth before. General experience from companies engaged in classical fermentation's learns that foreign growth does not necessarily have a negative impact on product quality.
18.37	–
18.38	–

18.4 Harvesting, Isolation and Purification

18.40	With reference to the remark in 18.15 the environment in which the down stream processing takes place need not always be supplied with a controlled quality of air. Also in this case normal hygienic conditions should be in place.
18.41	–
18.42	–
18.43	See 18.40 for products of classical fermentation.
18.44	–

18.5 Viral Removal/Inactivation steps

This subchapter is applicable to “biotechnological processes” only.	
18.50	–
18.51	–

18.52	–
18.53	–

Chapter 19 APIs for Use in Clinical Trials

19.1 General

This subject has been covered extensively in the APIC document "**GMP for API Development**" (<http://apic.cefic.org/framecommunica.html>). Some practical hints are included below.

19.10	There are many differences between the production of commercial APIs in a chemical plant and the production of chemical supply in a research /development facility. The research/development environment is characterised by limited information about process, analytical methods and data; also by work on a small scale and a high level of expertise of individuals involved. Making changes for process and product improvement is part of it's activities.
– 19.11	

19.2 Quality

19.20	A Quality Unit for the Development function should be in place, and also an SOP covering the quality system to be applied. Even if testing is performed outside the R&D function (other function in the company or an outside contractor) the responsibility for data gathered and recorded should remain inside the R&D function, assigned to the QU. All analytical results obtained should be recorded, checked and traceable. To allow traceability, a defined identification system should be in place. This can be based on a product unique code and a correlative batch number. Traceability should be checked at appropriate intervals, like milestone reviews. A labelling system, in accordance with the identification system in place, should be applied to each substance/sample.
– 19.25	

19.3 Equipment and Facilities

19.30	All equipment used in laboratory scale preparation should be appropriate to the task, in good working order, and clean. Lab equipment qualification (e.g. glassware) can't be expected. Qualification of pilot scale equipment should be considered. To minimise product contamination or cross contamination, appropriate measures should be taken into account. Some common lab operations, like vacuum filtering or drying in an oven where other products are also dried, are potentially sources of contamination or cross-contamination. Preventive measures should be in place when performing such operations, like covering with filter paper or other appropriate films.
– 19.31	

19.4 Control of Raw Materials

19.40	A systematic approach for raw materials reception, testing and acceptance / release decision should be in place. Beware that on-the-shelf reagents can be contaminated.
– 19.41	

19.5 Production

19.50 – 1951	Any deviation from normal operations should be documented. Process documentation should contain references to raw materials, chemical reaction / isolation pathway, process equipment, process parameters, any unexpected finding and obtained yields. When existing, process deviation investigations are recorded.

19.6 Validation

19.60 – 19.61	No validation is required because wording allows interpretation that validation is needed when more than “a single batch” is produced, and Development activities are by nature changing processes. The chemist may have an idea of which parameters are critical, but will not have performed the reaction enough times to establish the acceptable ranges. The information gathered during the development phase will become the foundation for the validation of the commercial process. Guidance on Cleaning Validation is given in the “GMP for R&D” document (reference see beginning of chapter 19).

19.7 Changes

19.70	Changes are part, as described above, of the development phase. Changes should be recorded for late information, but not subject to a formal change control system. The significance of the possible changes should be evaluated by scientists in other disciplines (toxicology, formulation, etc.), who use the API in the (new) drug development process.

19.8 Laboratory Controls

19.80 – 19.82	At early stages, product characteristics are often unknown. Testing methods based on sound scientific principles can be applied, and refined as knowledge is gained on products and their relevant properties. This information will become the foundation for setting the raw materials, API starting materials, the intermediates and API specifications. Sample retention should be defined and followed according to a plan. Samples are considered as part of the batch/experiment documentation. Expiry and retest dates are not relevant during development steps, but materials should be tested for its suitability prior to use. Data collected can afterwards justify process time limits (see 8.2).

19.9 Documentation

19.90	All process and testing relevant information should be available. A system for record keeping and archive should be in place. Data may be required to support registration.
–	
19.92	In addition to the records, process and analytical methods history should be also documented to justify the setting of ranges for critical points, and remain available for late evaluation. The basic information of process development should be selected, at the end of the research and development phase, and kept as long as the product is available commercially. Failed reactions records are useful information for the investigation of full scale batch failures.

Chapter 20 Glossary

Please refer to the original ICH Q7a document for any definitions!

Guidance for Industry

Process Validation: General Principles and Practices

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)**

**January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1**

Guidance for Industry

Process Validation: General Principles and Practices

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Guidance for Industry¹

Process Validation: General Principles and Practices

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance outlines the general principles and approaches that FDA considers appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients (APIs or drug substances), collectively referred to in this guidance as drugs or products. This guidance incorporates principles and approaches that all manufacturers can use to validate manufacturing processes.

This guidance aligns process validation activities with a product lifecycle concept and with existing FDA guidance, including the FDA/International Conference on Harmonisation (ICH) guidances for industry, *Q8(R2) Pharmaceutical Development*, *Q9 Quality Risk Management*, and *Q10 Pharmaceutical Quality System*.² Although this guidance does not repeat the concepts and principles explained in those guidances, FDA encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle.

¹ This guidance has been prepared by the Division of Manufacturing and Product Quality, Center for Drug Evaluation and Research (CDER), in cooperation with CDER's Office of Pharmaceutical Sciences, the Center for Biologics Evaluation and Research (CBER), the Office of Regulatory Affairs (ORA) and the Center for Veterinary Medicine (CVM) at the Food and Drug Administration.

² To make sure you have the most recent version of a guidance, check the CDER guidance page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, the CBER guidance page at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, or the CVM guidance page at <http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm>.

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The lifecycle concept links product and process development, qualification of the *commercial manufacturing process*,³ and maintenance of the process in a state of control during routine commercial production. This guidance supports process improvement and innovation through sound science.

This guidance covers the following categories of drugs:

- Human drugs
- Veterinary drugs
- Biological and biotechnology products
- Finished products and active pharmaceutical ingredients (APIs or drug substances)⁴
- The drug constituent of a combination (drug and medical device) product

This guidance does not cover the following types of products:

- Type A medicated articles and medicated feed
- Medical devices⁵
- Dietary supplements
- Human tissues intended for transplantation regulated under section 361 of the Public Health Service Act⁶

This guidance does not specify what information should be included as part of a regulatory submission. Interested persons can refer to the appropriate guidance or contact the appropriate Center in determining the type of information to include in a submission.

This guidance also does not specifically discuss the validation of automated process control systems (i.e., computer hardware and software interfaces), which are commonly integrated into modern drug manufacturing equipment. This guidance is relevant, however, to the validation of processes that include automated equipment in processing.

³ In this guidance, the term *commercial manufacturing process* refers to the manufacturing process resulting in *commercial product* (i.e., drug that is marketed, distributed, and sold or intended to be sold). For the purposes of this guidance, the term *commercial manufacturing process* does not include clinical trial or treatment IND material.

⁴ Separate current good manufacturing practice (CGMP) regulations for drug components such as APIs (drug substances) and intermediates have not published as of the date of this guidance, but these components are subject to the statutory CGMP requirements of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 351(a)(2)(B)). Process validation for APIs is discussed in the FDA/ICH guidance for industry, *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (ICH Q7), available on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. Section XII of ICH Q7 describes in detail the principles for validating API processes.

⁵ Guidance on process validation for medical devices is provided in a separate document, *Quality Management Systems – Process Validation*, edition 2, available at <http://www.ghrf.org/sg3/sg3-final.html>. See *infra* note 6.

⁶ See the FDA guidance for industry, *Validation of Procedures for Processing of Human Tissues Intended for Transplantation*, available on the Internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In the *Federal Register* of May 11, 1987 (52 FR 17638), FDA issued a notice announcing the availability of a guidance entitled *Guideline on General Principles of Process Validation* (the 1987 guidance).⁷ Since then, we have obtained additional experience through our regulatory oversight that allows us to update our recommendations to industry on this topic. This revised guidance conveys FDA's current thinking on process validation and is consistent with basic principles first introduced in the 1987 guidance. The revised guidance also provides recommendations that reflect some of the goals of FDA's initiative entitled "Pharmaceutical CGMPs for the 21st Century — A Risk-Based Approach," particularly with regard to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality system tools and concepts.⁸ This revised guidance replaces the 1987 guidance.

FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The CGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess (21 CFR 211.100(a) and 211.110(a)).

A. Process Validation and Drug Quality

Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. This principle incorporates the understanding that the following conditions exist:

- Quality, safety, and efficacy are designed or built into the product.
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.

⁷ The 1987 guidance was prepared by a working group that included representation from the Center for Devices and Radiological Health (CDRH). Since that time, CDRH elected to reference a process validation guidance prepared in cooperation with the Global Harmonization Task Force (GHTF). The principles and recommendations in that document, *Quality Management Systems – Process Validation*, edition 2 (available on the Internet at <http://www.ghet.org/sg3/sg3-final.html>) are also useful to consider for drug manufacturing processes.

⁸ See "Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach: Second Progress Report and Implementation Plan," available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/ucm071836.htm>.

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- Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.

B. Approach to Process Validation

For purposes of this guidance, *process validation* is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes process validation activities in three stages.

- Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

This guidance describes activities typical of each stage, but in practice, some activities might occur in multiple stages.

Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity, and potency. The assurance should be obtained from objective information and data from laboratory-, pilot-, and/or commercial-scale studies. Information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions.

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that results in products with the desired quality attributes. Manufacturers should:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product

Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the

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product. Focusing exclusively on qualification efforts without also understanding the manufacturing process and associated variations may not lead to adequate assurance of quality. After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change.⁹

Manufacturers should use ongoing programs to collect and analyze product and process data to evaluate the state of control of the process. These programs may identify process or product problems or opportunities for process improvements that can be evaluated and implemented through some of the activities described in Stages 1 and 2.

Manufacturers of legacy products can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their processes. Implementation of the recommendations in this guidance for legacy products and processes would likely begin with the activities described in Stage 3.

III. STATUTORY AND REGULATORY REQUIREMENTS FOR PROCESS VALIDATION

Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)), which states the following:

A drug . . . shall be deemed to be adulterated . . . if . . . the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

FDA regulations describing current good manufacturing practice (CGMP) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211.

The CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably. Process validation is required, in both general and specific terms, by the CGMP regulations in parts 210 and 211. The foundation for process validation is provided in § 211.100(a), which states that “[t]here shall be written procedures for production and process control *designed to assure* that the drug products have the identity, strength, quality, and purity they purport or are represented to possess...” (emphasis added). This regulation requires manufacturers to design a process, including operations and controls, which results in a product meeting these attributes.

⁹ The statute and regulations described in section III of this guidance explain the requirement that the methods and facilities used for the manufacturing of drugs be operated and administered under control sufficient to assure that the identity, strength, purity, and quality of a drug are as they purport or are represented to possess.

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Other CGMP regulations define the various aspects of validation. For example, § 211.110(a), *Sampling and testing of in-process materials and drug products*, requires that control procedures “. . . be established to monitor the output and *to validate* the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product” (emphasis added). Under this regulation, even well-designed processes must include in-process control procedures to assure final product quality. In addition, the CGMP regulations regarding sampling set forth a number of requirements for validation: samples must represent the batch under analysis (§ 211.160(b)(3)); the sampling plan must result in statistical confidence (§ 211.165(c) and (d)); and the batch must meet its predetermined specifications (§ 211.165(a)).

In addition to sampling requirements, the CGMP regulations also provide norms for establishing in-process specifications as an aspect of process validation. Section 211.110(b) establishes two principles to follow when establishing in-process specifications. The first principle is that “. . . in-process specifications for such characteristics [of in-process material and the drug product] shall be consistent with drug product final specifications” Accordingly, in-process material should be controlled to assure that the final drug product will meet its quality requirements. The second principle in this regulation further requires that in-process specifications “. . . shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate.” This requirement, in part, establishes the need for manufacturers to analyze process performance and control batch-to-batch variability.¹⁰

The CGMP regulations also describe and define activities connected with process design, development, and maintenance. Section 211.180(e) requires that information and data about product quality and manufacturing experience be periodically reviewed to determine whether any changes to the established process are warranted. Ongoing feedback about product quality and process performance is an essential feature of process maintenance.

In addition, the CGMP regulations require that facilities in which drugs are manufactured be of suitable size, construction, and location to facilitate proper operations (§ 211.42). Equipment must be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use (§ 211.63). Automated, mechanical, and electronic equipment must be calibrated, inspected, or checked according to a written program designed to assure proper performance (§ 211.68).

In summary, the CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably.

¹⁰ The Agency further explains this principle in the preamble to the final rule on “Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding” (43 FR 45013 at 45052, September 29, 1978) (available on the Internet at <http://www.fda.gov/cder/dmpq/preamble.txt>).

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IV. RECOMMENDATIONS

In the following sections, we describe general considerations for process validation, the recommended stages of process validation, and specific activities for each stage in the product lifecycle.

A. General Considerations for Process Validation

In all stages of the product lifecycle, good project management and good archiving that capture scientific knowledge will make the process validation program more effective and efficient. The following practices should ensure uniform collection and assessment of information about the process and enhance the accessibility of such information later in the product lifecycle.

- We recommend an integrated team approach¹¹ to process validation that includes expertise from a variety of disciplines (e.g., process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance). Project plans, along with the full support of senior management, are essential elements for success.
- Throughout the product lifecycle, various studies can be initiated to discover, observe, correlate, or confirm information about the product and process. All studies should be planned and conducted according to sound scientific principles, appropriately documented, and approved in accordance with the established procedure appropriate for the stage of the lifecycle.
- The terms *attribute(s)* (e.g., quality, product, component) and *parameter(s)* (e.g., process, operating, and equipment) are not categorized with respect to *criticality* in this guidance. With a lifecycle approach to process validation that employs risk based decision making throughout that lifecycle, the perception of criticality as a continuum rather than a binary state is more useful. All attributes and parameters should be evaluated in terms of their roles in the process and impact on the product or in-process material, and reevaluated as new information becomes available. The degree of control over those attributes or parameters should be commensurate with their risk to the process and process output. In other words, a higher degree of control is appropriate for attributes or parameters that pose a higher risk. The Agency recognizes that terminology usage can vary and expects that each manufacturer will communicate the meaning and intent of its terminology and categorization to the Agency.
- Many products are single-source or involve complicated manufacturing processes. Homogeneity within a batch and consistency between batches are goals of process validation activities. Validation offers assurance that a process is reasonably protected against sources of variability that could affect production output, cause supply problems, and negatively affect public health.

¹¹ This concept is discussed in more detail in FDA's guidance for industry, *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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B. Stage 1 — Process Design

Process design is the activity of defining the commercial manufacturing process that will be reflected in planned master production and control records. The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes.

1. Building and Capturing Process Knowledge and Understanding

Generally, early process design experiments do not need to be performed under the CGMP conditions required for drugs intended for commercial distribution that are manufactured during Stage 2 (process qualification) and Stage 3 (continued process verification). They should, however, be conducted in accordance with sound scientific methods and principles, including good documentation practices. This recommendation is consistent with ICH *Q10 Pharmaceutical Quality System*.¹² Decisions and justification of the controls should be sufficiently documented and internally reviewed to verify and preserve their value for use or adaptation later in the lifecycle of the process and product.

Although often performed at small-scale laboratories, most viral inactivation and impurity clearance studies cannot be considered early process design experiments. Viral and impurity clearance studies intended to evaluate and estimate product quality at commercial scale should have a level of quality unit oversight that will ensure that the studies follow sound scientific methods and principles and the conclusions are supported by the data.

Product development activities provide key inputs to the process design stage, such as the intended dosage form, the quality attributes, and a general manufacturing pathway. Process information available from product development activities can be leveraged in the process design stage. The functionality and limitations of commercial manufacturing equipment should be considered in the process design, as well as predicted contributions to variability posed by different component lots, production operators, environmental conditions, and measurement systems in the production setting. However, the full spectrum of input variability typical of commercial production is not generally known at this stage. Laboratory or pilot-scale models designed to be representative of the commercial process can be used to estimate variability.

Designing an efficient process with an effective process control approach is dependent on the process knowledge and understanding obtained. Design of Experiment (DOE) studies can help develop process knowledge by revealing relationships, including multivariate interactions, between the variable inputs (e.g., component characteristics¹³ or process parameters) and the resulting outputs (e.g., in-process material, intermediates, or the final product). Risk analysis tools can be used to screen potential variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained. The results of DOE studies can provide justification for establishing ranges of incoming component quality, equipment

¹² Available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

¹³ “*Component* means any ingredient [raw material] intended for use in the manufacture of a drug product, including those that may not appear in such drug product” (§ 210.3(b)(3)).

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parameters, and in-process material quality attributes. FDA does not generally expect manufacturers to develop and test the process until it fails.

Other activities, such as experiments or demonstrations at laboratory or pilot scale, also assist in evaluation of certain conditions and prediction of performance of the commercial process. These activities also provide information that can be used to model or simulate the commercial process. Computer-based or virtual simulations of certain unit operations or dynamics can provide process understanding and help avoid problems at commercial scale. It is important to understand the degree to which models represent the commercial process, including any differences that might exist, as this may have an impact on the relevance of information derived from the models.

It is essential that activities and studies resulting in process understanding be documented. Documentation should reflect the basis for decisions made about the process. For example, manufacturers should document the variables studied for a unit operation and the rationale for those variables identified as significant. This information is useful during the process qualification and continued process verification stages, including when the design is revised or the strategy for control is refined or changed.

2. Establishing a Strategy for Process Control

Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall. Strategies for process control can be designed to reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output), or combine both approaches.

Process controls address variability to assure quality of the product. Controls can consist of material analysis and equipment monitoring at significant processing points (§ 211.110(c)). Decisions regarding the type and extent of process controls can be aided by earlier risk assessments, then enhanced and improved as process experience is gained.

FDA expects controls to include both examination of material quality and equipment monitoring. Special attention to control the process through operational limits and in-process monitoring is essential in two possible scenarios:

1. When the product attribute is not readily measurable due to limitations of sampling or detectability (e.g., viral clearance or microbial contamination) or
2. When intermediates and products cannot be highly characterized and well-defined quality attributes cannot be identified.

These controls are established in the master production and control records (see § 211.186(a) and (b)(9)).

More advanced strategies, which may involve the use of process analytical technology (PAT), can include timely analysis and control loops to adjust the processing conditions so that the output remains constant. Manufacturing systems of this type can provide a higher degree of

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process control than non-PAT systems. In the case of a strategy using PAT, the approach to process qualification will differ from that used in other process designs. Further information on PAT processes can be found in FDA's guidance for industry on *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*.¹⁴

The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next stage for confirmation.

C. Stage 2 — Process Qualification

During the process qualification (PQ) stage of process validation, the process design is evaluated to determine if it is capable of reproducible commercial manufacture. This stage has two elements: (1) design of the facility and qualification of the equipment and utilities and (2) process performance qualification (PPQ). During Stage 2, CGMP-compliant procedures must be followed. Successful completion of Stage 2 is necessary before commercial distribution.¹⁵ Products manufactured during this stage, if acceptable, can be released for distribution.

1. Design of a Facility and Qualification of Utilities and Equipment

Proper design of a manufacturing facility is required under part 211, subpart C, of the CGMP regulations on *Buildings and Facilities*. It is essential that activities performed to assure proper facility design and commissioning precede PPQ. Here, the term *qualification* refers to activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly. These activities necessarily precede manufacturing products at the commercial scale.

Qualification of utilities and equipment generally includes the following activities:

- Selecting utilities and equipment construction materials, operating principles, and performance characteristics based on whether they are appropriate for their specific uses.
- Verifying that utility systems and equipment are built and installed in compliance with the design specifications (e.g., built as designed with proper materials, capacity, and functions, and properly connected and calibrated).
- Verifying that utility systems and equipment operate in accordance with the process requirements in all anticipated operating ranges. This should include challenging the equipment or system functions while under load comparable to that expected during

¹⁴ Available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. Other references that may be useful include ASTM E2474-06 "Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology" and ASTM E2476-09 "Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture."

¹⁵ As discussed in section III of this guidance, process validation (including process qualification) is legally enforceable under section 501(a)(2)(B) of the Act. FDA regulations require that process validation procedures be established and followed (§ 211.100) before a batch can be distributed (§§ 211.22 and 211.165).

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routine production. It should also include the performance of interventions, stoppage, and start-up as is expected during routine production. Operating ranges should be shown capable of being held as long as would be necessary during routine production.

Qualification of utilities and equipment can be covered under individual plans or as part of an overall project plan. The plan should consider the requirements of use and can incorporate risk management to prioritize certain activities and to identify a level of effort in both the performance and documentation of qualification activities. The plan should identify the following items:

1. the studies or tests to use,
2. the criteria appropriate to assess outcomes,
3. the timing of qualification activities,
4. the responsibilities of relevant departments and the quality unit, and
5. the procedures for documenting and approving the qualification.

The project plan should also include the firm's requirements for the evaluation of changes. Qualification activities should be documented and summarized in a report with conclusions that address criteria in the plan. The quality control unit must review and approve the qualification plan and report (§ 211.22).

2. Process Performance Qualification

The process performance qualification (PPQ) is the second element of Stage 2, process qualification. The PPQ combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected.

Success at this stage signals an important milestone in the product lifecycle. A manufacturer must successfully complete PPQ before commencing commercial distribution of the drug product.¹⁶ The decision to begin commercial distribution should be supported by data from commercial-scale batches. Data from laboratory and pilot studies can provide additional assurance that the commercial manufacturing process performs as expected.

The approach to PPQ should be based on sound science and the manufacturer's overall level of product and process understanding and demonstrable control. The cumulative data from all relevant studies (e.g., designed experiments; laboratory, pilot, and commercial batches) should be used to establish the manufacturing conditions in the PPQ. To understand the commercial process sufficiently, the manufacturer will need to consider the effects of scale. However, it is not typically necessary to explore the entire operating range at commercial scale if assurance can be provided by process design data. Previous credible experience with sufficiently similar products and processes can also be helpful. In addition, we strongly recommend firms employ

¹⁶ See section III of this guidance, Statutory and Regulatory Requirements for Process Validation.

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objective measures (e.g., statistical metrics) wherever feasible and meaningful to achieve adequate assurance.

In most cases, PPQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance than would be typical of routine commercial production. The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch. The increased level of scrutiny, testing, and sampling should continue through the process verification stage as appropriate, to establish levels and frequency of routine sampling and monitoring for the particular product and process. Considerations for the duration of the heightened sampling and monitoring period could include, but are not limited to, volume of production, process complexity, level of process understanding, and experience with similar products and processes.

The extent to which some materials, such as column resins or molecular filtration media, can be re-used without adversely affecting product quality can be assessed in relevant laboratory studies. The usable lifetimes of such materials should be confirmed by an ongoing PPQ protocol during commercial manufacture.

A manufacturing process that uses PAT may warrant a different PPQ approach. PAT processes are designed to measure in real time the attributes of an in-process material and then adjust the process in a timely control loop so the process maintains the desired quality of the output material. The process design stage and the process qualification stage should focus on the measurement system and control loop for the measured attribute. Regardless, the goal of validating any manufacturing process is the same: to establish scientific evidence that the process is reproducible and will consistently deliver quality products.

3. PPQ Protocol

A written protocol that specifies the manufacturing conditions, controls, testing, and expected outcomes is essential for this stage of process validation. We recommend that the protocol discuss the following elements:

- The manufacturing conditions, including operating parameters, processing limits, and component (raw material) inputs.
- The data to be collected and when and how it will be evaluated.
- Tests to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step.
- The sampling plan, including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination. Sampling during this stage should be more extensive than is typical during routine production.

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- Criteria and process performance indicators that allow for a science- and risk-based decision about the ability of the process to consistently produce quality products. The criteria should include:
 - A description of the statistical methods to be used in analyzing all collected data (e.g., statistical metrics defining both intra-batch and inter-batch variability).
 - Provision for addressing deviations from expected conditions and handling of nonconforming data. Data should not be excluded from further consideration in terms of PPQ without a documented, science-based justification.¹⁷
- Design of facilities and the qualification of utilities and equipment, personnel training and qualification, and verification of material sources (components and container/closures), if not previously accomplished.
- Status of the validation of analytical methods used in measuring the process, in-process materials, and the product.
- Review and approval of the protocol by appropriate departments and the quality unit.

4. PPQ Protocol Execution and Report

Execution of the PPQ protocol should not begin until the protocol has been reviewed and approved by all appropriate departments, including the quality unit. Any departures from the protocol must be made according to established procedure or provisions in the protocol. Such departures must be justified and approved by all appropriate departments and the quality unit before implementation (§ 211.100).

The commercial manufacturing process and routine procedures must be followed during PPQ protocol execution (§§ 211.100(b) and 211.110(a)). The PPQ lots should be manufactured under normal conditions by the personnel routinely expected to perform each step of each unit operation in the process. Normal operating conditions should include the utility systems (e.g., air handling and water purification), material, personnel, environment, and manufacturing procedures.

A report documenting and assessing adherence to the written PPQ protocol should be prepared in a timely manner after the completion of the protocol. This report should:

- Discuss and cross-reference all aspects of the protocol.
- Summarize data collected and analyze the data, as specified by the protocol.

¹⁷ For additional guidance regarding out-of-specification results, see FDA's Guidance for Industry, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070287.pdf>.

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- Evaluate any unexpected observations and additional data not specified in the protocol.
- Summarize and discuss all manufacturing nonconformances such as deviations, aberrant test results, or other information that has bearing on the validity of the process.
- Describe in sufficient detail any corrective actions or changes that should be made to existing procedures and controls.
- State a clear conclusion as to whether the data indicates the process met the conditions established in the protocol and whether the process is considered to be in a state of control. If not, the report should state what should be accomplished before such a conclusion can be reached. This conclusion should be based on a documented justification for the approval of the process, and release of lots produced by it to the market in consideration of the entire compilation of knowledge and information gained from the design stage through the process qualification stage.
- Include all appropriate department and quality unit review and approvals.

D. Stage 3 — Continued Process Verification

The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal.

Adherence to the CGMP requirements, specifically, the collection and evaluation of information and data about the performance of the process, will allow detection of undesired process variability. Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control (§ 211.180(e)).

An ongoing program to collect and analyze product and process data that relate to product quality must be established (§ 211.180(e)). The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process.

We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability.¹⁸ Procedures should describe

¹⁸ Some references that may be useful include the following: ASTM E2281-03 “Standard Practice for Process and Measurement Capability Indices,” ASTM E2500-07 “Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment,” and ASTM E2709-09 “Standard Practice for Demonstrating Capability to Comply with a Lot Acceptance Procedure.” This is not a complete list of all useful references on this topic. Many industry standards, books, and guides on these topics are available.

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how trending and calculations are to be performed and should guard against overreaction to individual events as well as against failure to detect unintended process variability. Production data should be collected to evaluate process stability and capability. The quality unit should review this information. If properly carried out, these efforts can identify variability in the process and/or signal potential process improvements.

Good process design and development should anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits. However, a process is likely to encounter sources of variation that were not previously detected or to which the process was not previously exposed. Many tools and techniques, some statistical and others more qualitative, can be used to detect variation, characterize it, and determine the root cause. We recommend that the manufacturer use quantitative, statistical methods whenever appropriate and feasible. Scrutiny of intra-batch as well as inter-batch variation is part of a comprehensive continued process verification program under § 211.180(e).

We recommend continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until sufficient data are available to generate significant variability estimates. These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process. Monitoring can then be adjusted to a statistically appropriate and representative level. Process variability should be periodically assessed and monitoring adjusted accordingly.

Variation can also be detected by the timely assessment of defect complaints, out-of-specification findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports. Production line operators and quality unit staff should be encouraged to provide feedback on process performance. We recommend that the quality unit meet periodically with production staff to evaluate data, discuss possible trends or undesirable process variation, and coordinate any correction or follow-up actions by production.

Data gathered during this stage might suggest ways to improve and/or optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges and set-points), process controls, component, or in-process material characteristics. A description of the planned change, a well-justified rationale for the change, an implementation plan, and quality unit approval before implementation must be documented (§ 211.100). Depending on how the proposed change might affect product quality, additional process design and process qualification activities could be warranted.¹⁹

Maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in control. Once established, qualification status must be maintained through routine monitoring, maintenance, and calibration procedures and schedules (21 CFR part 211,

¹⁹ Certain manufacturing changes may call for formal notification to the Agency before implementation, as directed by existing regulations (see, e.g., 21 CFR 314.70 and 601.12).

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subparts C and D). The equipment and facility qualification data should be assessed periodically to determine whether re-qualification should be performed and the extent of that re-qualification. Maintenance and calibration frequency should be adjusted based on feedback from these activities.

V. CONCURRENT RELEASE OF PPQ BATCHES

In most cases, the PPQ study needs to be completed successfully and a high degree of assurance in the process achieved before commercial distribution of a product. In special situations, the PPQ protocol can be designed to release a PPQ batch for distribution before complete execution of the protocol steps and activities, i.e., concurrent release. FDA expects that concurrent release will be used rarely.

Concurrent release might be appropriate for processes used infrequently for various reasons, such as to manufacture drugs for which there is limited demand (e.g., orphan drugs, minor use and minor species veterinary drugs) or which have short half lives (e.g., radiopharmaceuticals, including positron emission tomography drugs). Concurrent release might also be appropriate for drugs that are medically necessary and are being manufactured in coordination with the Agency to alleviate a short supply.

Conclusions about a commercial manufacturing process can only be made after the PPQ protocol is fully executed and the data are fully evaluated. If Stage 2 qualification is not successful (i.e., does not demonstrate that the process as designed is capable of reproducible performance at commercial scale), then additional design studies and qualification may be necessary. The new product and process understanding obtained from the unsuccessful qualification study(ies) can have negative implications if any lot was already distributed. Full execution of Stages 1 and 2 of process validation is intended to preclude or minimize that outcome.

Circumstances and rationale for concurrent release should be fully described in the PPQ protocol. Even when process performance assessment based on the PPQ protocol is still outstanding, any lot released concurrently must comply with all CGMPs, regulatory approval requirements, and PPQ protocol lot release criteria. Lot release under a PPQ protocol is based upon meeting confidence levels appropriate for each quality attribute of the drug.

When warranted and used, concurrent release should be accompanied by a system for careful oversight of the distributed batch to facilitate rapid customer feedback. For example, customer complaints and defect reports should be rapidly assessed to determine root cause and whether the process should be improved or changed. Concurrently released lots must also be assessed in light of any negative PPQ study finding or conclusions and appropriate corrective action must be taken (§§ 211.100(a), 211.180(e), and 211.192). We recommend that each batch in a concurrent release program be evaluated for inclusion in the stability program. It is important that stability test data be promptly evaluated to ensure rapid detection and correction of any problems.

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VI. DOCUMENTATION

Documentation at each stage of the process validation lifecycle is essential for effective communication in complex, lengthy, and multidisciplinary projects. Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each stage of the lifecycle. Information transparency and accessibility are fundamental tenets of the scientific method. They are also essential to enabling organizational units responsible and accountable for the process to make informed, science-based decisions that ultimately support the release of a product to commerce.

The degree and type of documentation required by CGMP vary during the validation lifecycle. Documentation requirements are greatest during Stage 2, process qualification, and Stage 3, continued process verification. Studies during these stages must conform to CGMPs and must be approved by the quality unit in accordance with the regulations (see §§ 211.22 and 211.100). Viral and impurity clearance studies, even when performed at small scale, also require quality unit oversight.

CGMP documents for commercial manufacturing (i.e., the initial commercial master batch production and control record (§ 211.186) and supporting procedures) are key outputs of Stage 1, process design. We recommend that firms diagram the process flow for the full-scale process. Process flow diagrams should describe each unit operation, its placement in the overall process, monitoring and control points, and the component, as well as other processing material inputs (e.g., processing aids) and expected outputs (i.e., in-process materials and finished product). It is also useful to generate and preserve process flow diagrams of the various scales as the process design progresses to facilitate comparison and decision making about their comparability.

VII. ANALYTICAL METHODOLOGY

Process knowledge depends on accurate and precise measuring techniques used to test and examine the quality of drug components, in-process materials, and finished products. Validated analytical methods are not necessarily required during product- and process-development activities or when used in characterization studies. Nevertheless, analytical methods should be scientifically sound (e.g., specific, sensitive, and accurate) and provide results that are reliable. There should be assurance of proper equipment function for laboratory experiments. Procedures for analytical method and equipment maintenance, documentation practices, and calibration practices supporting process-development efforts should be documented or described. New analytical technology and modifications to existing technology are continually being developed and can be used to characterize the process or the product. Use of these methods is particularly appropriate when they reduce risk by providing greater understanding or control of product quality. However, analytical methods supporting commercial batch release must follow CGMPs in parts 210 and 211. Clinical supply production should follow the CGMPs appropriate for the particular phase of clinical studies.

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GLOSSARY

Capability of a process: Ability of a process to produce a product that will fulfill the requirements of that product. The concept of process capability can also be defined in statistical terms. (ISO 9000:2005)

Commercial manufacturing process: The manufacturing process resulting in commercial product (i.e., drug that is marketed, distributed, and sold or intended to be sold). For the purposes of this guidance, the term *commercial manufacturing process* does not include clinical trial or treatment IND material.

Concurrent release: Releasing for distribution a lot of finished product, manufactured following a qualification protocol, that meets the lot release criteria established in the protocol, but before the entire study protocol has been executed.

Continued process verification: Assuring that during routine production the process remains in a state of control.

Performance indicators: Measurable values used to quantify quality objectives to reflect the performance of an organization, process or system, also known as *performance metrics* in some regions. (ICH Q10)

Process design: Defining the commercial manufacturing process based on knowledge gained through development and scale-up activities.

Process qualification: Confirming that the manufacturing process as designed is capable of reproducible commercial manufacturing.

Process validation: The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

Quality: The degree to which a set of inherent properties of a product, system, or process fulfils requirements. (ICH Q9)

State of control: A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)

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- FDA, (CDER, CVM, and ORA), *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, guidance for industry, September 2004.
- FDA, (CDER, CBER, CVM, and ORA), *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*, guidance for industry, September 2006.
- FDA/Global Harmonization Task Force (GHTF; medical devices), *Quality Management Systems – Process Validation*, edition 2, guidance, January 2004.
- FDA/ICH, (CDER and CBER), *Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients*, guidance for industry, August 2001.
- FDA/ICH, (CDER and CBER), *Q8(R2) Pharmaceutical Development*, guidance for industry, November 2009.
- FDA/ICH, (CDER and CBER), *Q9 Quality Risk Management*, guidance for industry, June 2006.
- FDA/ICH (CDER and CBER) *Q10 Pharmaceutical Quality System*, guidance for industry, April 2009.
- ASTM E2474-06 Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology.
- ASTM E2476-09 Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture.
- ASTM E2281-03 Standard Practice for Process and Measurement Capability Indices.
- ASTM E2500-07 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment.
- ASTM E2709-10 Standard Practice for Demonstrating Capability to Comply with a Lot Acceptance Procedure.

Guidance Agenda: New & Revised Draft Guidances CDER is Planning to Publish During Calendar Year 2011

(See the Good Guidance Practices (GGPs) regulation on this Web page or
21 CFR 10.115 for details about the Guidance Agenda.)

CATEGORY — Advertising

- Amendment of the Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements
- Comparative Claims in Prescription Drug and Medical Device Promotion
- Direct to Consumer Television Advertisements - FDAAA DTC Television Pre-Review Program
- Responding to Unsolicited Requests for Prescription Drug and Medical Device Information, Including Those Encountered on the Internet.

CATEGORY – Biopharmaceutics

- Bioavailability and Bioequivalence Studies for Orally Administered Drug Products Submitted in New Drug Applications; General Consideration
- Food-Effect Bioavailability Studies for Orally Administered Drug Products

CATEGORY — Chemistry

- Bioequivalence Studies with Pharmacokinetic Endpoints for Drug Products Submitted in Abbreviated New Drug Applications
- Comparability Protocols for Approved Drugs: Chemistry, Manufacturing, and Controls Information
- Immunogenicity Considerations for Low Molecular Weight Heparin
- Liposome Drug Products: CMC, Human Pharmacokinetic and Bioavailability; and Labeling Documentation
- Nongovernment Standards
- Size of Beads in Drug Products Labeled for Sprinkle
- Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation

CATEGORY — Clinical/Medical

- Clinical Endpoints for the Approval of Non-Small Cell Lung Cancer
- Pregnant Women in Clinical Trials – Scientific and Ethical Considerations
- Monitoring of Clinical Investigator Conduct and Oversight of Clinical Investigations of Human Drugs, Devices and Biological Products.
- Standards for Clinical Trial Imaging Endpoints

CATEGORY — Clinical Pharmacology

- Bioanalytical Methods Validation
- Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies
- Clinical Pharmacology Consideration for Therapeutics Proteins
- General Clinical Pharmacology Considerations for Pediatrics Studies for Drugs and Biological Products
- Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling
- Development of Extended Released Formulations
- Use of Histopathology in Biomarker Qualification Studies

CATEGORY — Clinical/Statistical

- Multiple Endpoints

CATEGORY — Combination Products

- Development of Drugs in Combination

CATEGORY — Current Good Manufacturing Practices (CGMPs)/Compliance

- Contract Manufacturing
- Control of Components
- Control of Highly Potent Compounds
- Expiration Dating of Unit-Dose Repackaged Drugs: Compliance Policy Guide
- Importation of Active Pharmaceutical Ingredients (API) for Use in Human Drugs
- Medical Gases, General CGMP
- Non-Penicillin Beta-Lactam Contamination
- Outsourcer Pharmacy Operations Compliance Policy Guide
- Pharmaceutical Component Quality Control
- Pharmaceutical Manufacturing Statistics
- Pre-Launch Activities Importation Request (PLAIR)
- Prevention and Control of Viral Contamination
- Validation of Air Separation Processes for Medical Gas
- Heparin for Drug and Medical Device Use: Testing for Oversulfated Chondroitin Sulfate Contamination in Crude Heparin
- Compliance Policy Guide Section 490.200 for FDA Staff: Parametric Release - Drug Products Terminally Sterilized by Moist Heat
- Pharmacy Compounding of Human Drugs Under Section 503A of the Federal Food, Drug, and Cosmetic Act
- Good Pharmacy Compounding Practices for Sterile Drug Products
- Compounding Drug Products for the Use in Practitioners Offices

CATEGORY — Drug Safety Information

- Best Practices for Conducting and Reporting Pharmacoeconomic Safety Studies Using Electronic Healthcare Data
- Naming, Labeling, and Packaging Practices to Reduce Medication Errors

CATEGORY — Electronic Submissions

- Electronic Submission of Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions
- Providing Regulatory Submissions in Electronic Format – Analysis Datasets and Documentation

CATEGORY — IND

- Adverse Events: Collection and Reporting for Secondary Endpoints
- Good Review Management Principles and Practices for Effective IND Development and Review

CATEGORY – OTC

- Self-Selection Studies for Non Prescription Drug Products

CATEGORY — Labeling

- Drug Names and Dosage Forms
- Indications and Usage Section of Labeling
- Pediatric Information: Incorporating into Human Prescription Drug and Biological Products Labeling
- Organ-Specific Warnings: Internal Analgesic, Antipyretic and Antirheumatic Drug Products for Over-the-Counter Human Use-Labeling of Products That Contain Acetaminophen

CATEGORY — Procedural

- Investigational New Drug Applications prepared and submitted by Clinical Sponsor Investigators
- Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act of 2007 (BPCA)
- Pediatric Studies: How to Comply with the Pediatric Research Equity Act, Title IV of the Food and Drug Administration Amendments Act of 2007

Note: Agenda items reflect guidances under development as of the date of this posting.

Guidance for Industry

Non-Penicillin Beta-Lactam Risk Assessment: A CGMP Framework

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Edwin Melendez 301-796-3284.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**March 2011
Current Good Manufacturing Practices (CGMPs)**

Guidance for Industry

Non-Penicillin Beta-Lactam Risk Assessment: A CGMP Framework

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**March 2011
Current Good Manufacturing Practices (CGMP)**

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Guidance for Industry¹

**Non-Penicillin Beta-Lactam Risk Assessment:
A CGMP Framework**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance describes the importance of implementing appropriate steps during the manufacturing process to prevent cross-contamination of finished pharmaceuticals and active pharmaceutical ingredients (APIs) with non-penicillin beta-lactam antibiotics. This guidance also provides information regarding the relative health risk of, and the potential for, cross-reactivity in the classes of sensitizing beta-lactams (penicillins and non-penicillin beta-lactams). This guidance is intended to assist manufacturers in assessing whether separate facilities should be used based on the relative health risk of cross-reactivity.

Drug cross-contamination is the contamination of one drug with one or more different drugs. Penicillin can be a sensitizing agent that triggers a hypersensitive exaggerated allergic immune response in some people. Accordingly, developing strategies to prevent cross-contamination of other drugs with penicillin is a key element of manufacturing penicillin. Non-penicillin beta-lactam drugs may also be sensitizing agents, and cross-contamination with non-penicillin beta-lactam drugs can initiate drug-induced hypersensitivity reactions, including anaphylaxis, an allergic reaction that may be a life-threatening event. As with penicillin, a critical aspect of manufacturing non-penicillin beta-lactam drugs is preventing cross-contamination to reduce the potential for drug-induced, life-threatening allergic reactions.

The information in this guidance is intended for manufacturers of finished pharmaceuticals and APIs, including repackagers. Other establishments that handle drugs, such as pharmacy compounders, may find this information useful.

¹ This guidance was developed by the Office of Compliance, Division of Manufacturing and Product Quality, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) requires that, with few exceptions, all drugs be manufactured in compliance with current good manufacturing practices (CGMPs). Drugs that are not in compliance with CGMPs are considered to be adulterated. Furthermore, finished pharmaceuticals are required to comply with the CGMP regulations at 21 CFR parts 210 and 211.

Several CGMP regulations directly address facility and equipment controls and cleaning. For example, § 211.42(c) requires building and facility controls in general to prevent cross-contamination of drug products. Specifically, the regulation states, “[t]here shall be separate or defined areas or such other control systems for the firm’s operations as are necessary to prevent contamination or mix-ups” during manufacturing, processing, packaging, storage, and holding processes.

With respect to penicillin, § 211.42(d) requires that “[o]perations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.” However, FDA has clarified that separate buildings may not be necessary, provided that the section of the manufacturing facility dedicated to manufacturing penicillin is structurally isolated (i.e., completely and comprehensively separated) from the areas of the facility in which non-penicillin products are manufactured.² Under § 211.46(d), manufacturers must completely separate air handling systems for penicillin from those used for other drugs for human use. Similarly, § 211.176 requires manufacturers to test non-penicillin drug products for penicillin where the possibility of exposure to cross-contamination exists, and prohibits manufacturers from marketing such products if detectable levels of penicillin are found.³

Although FDA has not issued CGMP regulations specific to APIs, the Agency has provided guidance to API manufacturers in the guidance for industry, ICH⁴ Q7, *Good Manufacturing*

² Preamble to the final rule, “Current Good Manufacturing Practice, Processing, Packing, or Holding,” published in the FEDERAL REGISTER of September 29, 1978 (43 FR 45014 at 45038).

³ See “A Review of Procedures for the Detection of Residual Penicillins in Drugs” (Appendix I, *Procedures for Detecting and Measuring Penicillin Contamination in Drugs*, FDA By-Lines No. 8 (November 1977)), available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM095812.pdf>.

⁴ International Conference on Harmonization.

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Practice Guidance for Active Pharmaceutical Ingredients (ICH Q7 guidance).⁵ Because some APIs are sensitizing compounds that may cause anaphylactic shock, preventing cross-contamination in APIs is as important as preventing cross-contamination in finished products. The ICH Q7 guidance recommends using dedicated production areas, which can include facilities, air handling equipment, and/or processing equipment, in the production of highly sensitizing materials, such as penicillins and cephalosporins.⁶

Beta-lactam antibiotics share a basic chemical structure that includes a three-carbon, one-nitrogen cyclic amine structure known as the beta-lactam ring. The side chain associated with the beta-lactam ring is a variable group attached to the core structure by a peptide bond. The side chain variability contributes to antibacterial activity.

As of the date of this publication, FDA has approved over 34 beta-lactam compounds as active ingredients in drugs for human use.⁷ Beta-lactam antibiotics include the following five classes:

- penicillins (e.g., ampicillin, oxacillin)
- cephalosporins (e.g., cephalexin, cefaclor)
- penems (e.g., imipenem, meropenem)
- carbacephems (e.g., loracarbef)
- monobactams (e.g., aztreonam)⁸

The penicillins, cephalosporins, penems, and carbacephems share a characteristic bicyclic core structure, which is believed to initiate allergic reactions. The monobactam aztreonam has a unique monocyclic beta-lactam nucleus and rarely cross-reacts with penicillins and cephalosporins.⁹ Aztreonam and ceftazidime have a common side chain, and cross-reactivity between aztreonam and ceftazidime has been reported.¹⁰

⁵ We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the Guidance Page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁶ See section IV.D Containment (4.4) of the ICH Q7 guidance.

⁷ Approved beta-lactam antibiotics are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, generally known as the *Orange Book* (available on the Internet at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>). The Orange Book is searchable by active ingredient and updated as newer drug products are added.

⁸ Yao, JDC, and RC Moellering, Jr., Antibacterial agents, in *Manual of Clinical Microbiology*, 9th edition, edited by PR Murray et al., Washington D.C., ASM Press, 2007.

⁹ American Academy of Allergy, Asthma, and Immunology, 1999, Disease management of drug hypersensitivity: a practice parameter, *Ann Allergy Asthma Immunol*, 83(supp): S665-S700.

¹⁰ Perez Pimiento, A, M Gomez Martinez, A Minguez Mena, A Trampal Gonzalez, S de Paz Arranz, and M Rodriguez Mosquera, 1998, Aztreonam and ceftazidime: evidence of in vivo cross-allergenicity, *Allergy*, 53:624-625.

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Beta-lactam antibiotics inhibit bacterial cell wall synthesis. Many bacteria produce beta-lactamases, which are enzymes that degrade and inactivate beta-lactam antibiotics. Beta-lactam compounds such as clavulanic acid, tazobactam, and sulbactam have weak antibacterial activity but are irreversible inhibitors of many beta-lactamases; they are used in combination with specific beta-lactam agents to preserve antibacterial activity.

Allergic reactions associated with penicillins and non-penicillin beta-lactam antibiotics range from rashes to life-threatening anaphylaxis. Immunoglobulin E (IgE) antibodies mediate the immediate hypersensitivity reactions that are responsible for the symptoms of hay fever, asthma, hives, and anaphylactic shock. IgE-mediated hypersensitivity reactions are of primary concern because they may be associated with significant morbidity and mortality. There is evidence that patients with a history of hypersensitivity to penicillin may also experience IgE-mediated reactions to cephalosporins and penems.¹¹ Cross-reactivity (cross-sensitivity) between beta-lactam products has been and continues to be a major concern in the manufacture of drugs.

All non-penicillin beta-lactam antibiotics also have the potential to sensitize individuals, and subsequent exposure to penicillin may result in severe allergic reactions in some patients. Although the frequency of hypersensitivity reactions due to cross-reactivity between beta-lactam classes can be lower than the risk within a class,¹² the hazard posed is present¹³ and potentially life-threatening. The potential health hazard of non-penicillin beta-lactam drugs is therefore similar to that of penicillins. Further similarities between non-penicillin beta-lactam antibiotics and penicillins are as follows:

- It is difficult to define the minimal dose below which allergic responses are unlikely to occur in humans.¹⁴
- There is a lack of suitable animal or receptor testing models that are predictive of human sensitivity.¹⁵
- The threshold dose at which allergenic response could occur is extremely low and

¹¹ Saxon, A, DC Adelman, A Patel, R Hajdu, and GB Calandra, 1988, Imipenem cross-reactivity with penicillin in humans, *J Allergy Clin Immunol*, 82:213-217; Saxon, A, GN Beall, AS Rohr, and DC Adelman, 1987, Immediate hypersensitivity reactions to beta-lactam antibiotics, *Ann Intern Med*, 107(2):204-215; Prescott, Jr., WA, DD DePestel, JJ Ellis, and RE Regal, 2004, Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy, *Clin Infect Dis*, 38:1102-1107.

¹² Salkind, AR, PG Cuddy, and JW Foxworth, 2001, Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy, *JAMA*, 285:2498-2505.

¹³ Khan, D. and R Solensky, 2010, Drug Allergy, *J Allergy Clin Immunol*. 125(2): S131.

¹⁴ Dayan, AD, 1993, Allergy to antimicrobial residues in food: assessment of the risk to man, *Vet Microbiol*, 35:213-226; Blanca, M, J Garcia, JM Vega, A Miranda, MJ Carmona et al., 1996, Anaphylaxis to penicillins after non-therapeutic exposure: an immunological investigation, *Clin Exp Allergy*, 26:335-340.

¹⁵ Olson, H, G Betton, D Robinson, K Thomas, A Monro et al., 2000, Concordance of the toxicity of pharmaceuticals in humans and in animals, *Regul Toxicol Pharmacol*, 32:56-67.

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difficult to detect with current analytical methods.¹⁶

Some beta-lactam intermediate compounds and derivatives possess sensitization and cross-reactivity properties. Beta-lactam chemical manufacturing processes including, but not limited to, fermentation and synthesis may create beta-lactam intermediates or derivatives with unknown health consequences. Therefore, the health risk of sensitization and cross-reaction is difficult to predetermine for beta-lactam intermediates, and is not always well-defined.

Beta-lactam intermediate compounds are usually API precursor materials that undergo molecular change or purification before use in the manufacture of beta-lactam antibiotic APIs. As a result of these changes, the intermediate compounds may develop antigenic characteristics that can produce allergic reactions. For example, 6-aminopenicillanic acid (6-APA) serves as the intermediate for the formation of all synthetic penicillins that are formed by attaching various side chains. The structure of 6-APA includes unbroken beta-lactam and thiazolidine rings. The beta-lactam ring is relatively unstable, and it commonly breaks open. In the case of 6-APA, this breakage leads to the formation of a penicilloyl moiety, which is also known as the major antigenic determinant of penicillin. This moiety is thought to be a common cause of penicillin urticarial reaction.¹⁷ Degradation of 6-APA can also result in the formation of minor antigenic determinants, including penicilloic acids, penaldic acid, and penicillamine. Anaphylactic reactions to penicillins are usually due to IgE antibodies to minor determinants. Therefore, although 6-APA is not a true antibiotic, it still carries with it a potential to induce allergenicity.

Derivatives are unintended by-products that occur during the manufacturing process (i.e., an impurity or degradant) which could have sensitizing properties. Similar to intermediates, beta-lactam derivatives may also develop antigenic properties that can produce allergic reactions.

Beta-lactam antibiotics are similar to one another in many ways, but they may differ in pharmacokinetics, antibacterial activity, and potential to cause serious allergic reactions. Because allergy testing methods have not been well-validated,¹⁸ it is clinically difficult to determine the occurrence and rate of cross-reactivity between beta-lactam antibiotics in humans. Therefore, undiagnosed or underreported cases of cross-reactivity likely exist. Some beta-lactam antibiotics have negligible potential for cross-reactivity with beta-lactams of other classes, whereas other beta-lactam compounds may exhibit sensitizing activity as derivatives before the incorporation of side chains that confer antibacterial activity.

¹⁶ Perez Pimiento, A, M Gomez Martinez, A Minguez Mena, A Trampal Gonzalez, S de Paz Arranz, and M Rodriguez Mosquera, 1998, Aztreonam and ceftazidime: evidence of in vivo cross-allergenicity, *Allergy*, 53:624-625; Shepard, GM, 1991, Allergy to B-lactam antibiotics, *Immunol Allergy Clin North Am*, 11(3):611-633.

¹⁷ Middleton Principle of Allergy and Immunology: Principles and Practice, 2009 edition, chapter 68: Drug Allergy, electronic book version, at the sentence above Figure 68.2.

¹⁸ Bernstein, IL, JT Li, DI Bernstein, et al., 2008, Allergy diagnostic testing: an updated practice parameter, *Ann Allergy Asthma Immunol*, 100:S1-S148.

Contains Nonbinding Recommendations

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III. RECOMMENDATIONS

Because of the health risks associated with cross-reactivity (cross-sensitivity) of beta-lactams, non-beta-lactam manufacturers should assess and establish stringent controls (including appropriate facility design provisions assuring separation) to prevent cross-contamination. Just as FDA considers the separation of production facilities for penicillins to be current good manufacturing practice, FDA expects manufacturers to treat sensitizing non-penicillin beta-lactam-based products similarly. Specifically, FDA recommends that manufacturers establish appropriate separation and control systems designed to prevent the following types of cross-contamination:

- Non-penicillin beta-lactam contamination in a non-beta-lactam product (e.g., cefaclor in aspirin)
- Non-penicillin beta-lactam contamination in another non-penicillin beta-lactam (e.g., cephalexin in imipenem)

As with penicillin, the section of a facility dedicated to manufacturing a sensitizing non-penicillin beta-lactam should be structurally isolated (i.e., completely and comprehensively separated) from areas in the facility in which other products are manufactured. This control applies to each of the five classes of sensitizing beta-lactams; the area in which any class of sensitizing beta-lactam is manufactured should be separated from areas in which any other products are manufactured, including any other class of sensitizing beta-lactam or any other non-beta-lactam product. Manufacturing that is restricted to a specific class of beta-lactam compound (e.g., the cephalosporin family of products) would generally not mandate separate facilities and air handling systems, and could permit production campaigning and cleaning as sufficient control.

SUBJECT: INSPECTION OF MEDICAL DEVICE MANUFACTURERS		IMPLEMENTATION DATE February 2, 2011
		COMPLETION DATE February 2, 2015
DATA REPORTING		
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES	
73-91	82845A; 42845A	All Level 1 (Abbreviated) Inspections
	82845B; 42845B	All Level 2 (Comprehensive) Inspections
	82845C; 42845C	All Level 3 (Compliance Follow-up) Inspections
	82845G	All For Cause Inspections
	82845H	Risk Based Work Plan Inspections
	82845P	Joint FDA/Accredited Person Inspections
	82845S	Report Time spent on Assessment of Firm's Sterilization processes
	81010	Report Time spent on MDR Follow-up
	81011	Report Time spent on Assessment of Firm's MDR Practices
	81845T	Report Time spent on Assessment of Firm's Tracking Practices
	81845R	Report Time spent on Assessment of Firm's Corrections and Removals Practices
	82A800	Independent Accredited Person Inspections

* Previous editions obsolete.

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Attachment D	Summary of Tracking Requirements
Attachment E	Summary of Corrections and Removals Requirements

Field Reporting Requirements

EIRs: All recommendations for administrative/regulatory action should include the EIR, FDA-483 and exhibits. The recommendations should be sent to the Center for Devices and Radiological Health (CDRH) and for tissue or combination products the recommendations should also be sent to the Center for Biologics Evaluation and Research (CBER) and/or the Center for Drug Evaluation and Research (CDER) as appropriate.

Note: If the district wishes to obtain comment from CDRH for any EIR, the district should attach a cover memorandum to the EIR outlining the issues to be considered by the Office of Compliance (OC) or Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD).

This guidance document represents the agency's current thinking on the enforcement of the Quality System (QS), Medical Device Reporting (MDR), Medical Device Tracking, Corrections and Removals, and the Registration and Listing regulations. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

PAC Guidance

PROGRAM	PACs
Quality System	Level 1 (82845A)
	Level 2 (82845B)
	Level 3 (82845C)
For Cause	82845G
Risk Based Work Plan	82845H
Joint FDA/Accredited Persons	82845P
Independent Accredited Person Inspection	82A800
MDR	81010 & 81011
Tracking	81845T
CAR	81845R
Sterilization Inspections	82845S

Note: When conducting sterilization review as part of the Production and Process Controls subsystem, report **only** the time spent reviewing the sterilization process during the Quality System inspection, if covered under PAC 82845S. Also, report PACs, 81010, 81011, 81845T and 81845R, as applicable.

The above PAC Guidance is provided for investigator reference only. Additional CBER and/or CDER PAC codes may also be necessary for multi-jurisdictional products (i.e. tissue and combination products). Please refer to the inspection assignment for guidance.

PART I

BACKGROUND

This compliance program provides guidance to FDA field and center staffs for the inspections and administrative/enforcement activities related to the Quality System (QS) regulation (21 CFR Part 820), the Medical Device Reporting (MDR) regulation (21 CFR Part 803), the Medical Device Tracking regulation (21 CFR Part 821), the Corrections and Removals regulation (21 CFR Part 806), and the Registration and Listing regulation (21 CFR Part 807). This compliance program supersedes the program of the same name which was issued on June 15, 2006.

This compliance program encompasses five regulations for inspecting medical device firms. Under the QS regulation, manufacturers are expected to control their devices from design stage through post-market surveillance. Manufacturing processes, such as sterilization, are required to be implemented under appropriate controls. The MDR, Tracking, and Corrections and Removals regulations involve activities with which manufacturers and importers are required to comply after the devices are distributed. This compliance program provides specific guidance for each. It also requires coverage for the Registration & Listing regulation.

A. THE QUALITY SYSTEM (QS) REGULATION

Manufacturers establish and follow quality systems to help ensure that their products consistently meet applicable requirements and specifications. The quality systems for FDA-regulated products (food, drugs, biologics, and devices) are known as Current Good Manufacturing Practices (CGMP's). CGMP requirements for devices in part 820 (21 CFR part 820) were first authorized by section 520(f) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(f)), which was among the authorities added to the act by the Medical Device Amendments of 1976. Under section 520(f) of the act, FDA issued a final rule in the Federal Register of July 21, 1978 (43 FR 31 508), prescribing CGMP requirements for the methods used in, and the facilities and controls used for the manufacture, packing, storage, and installation of medical devices. This regulation became effective on December 18, 1978.

The Safe Medical Devices Act of 1990 (the SMDA), enacted on November 28, 1990, amended section 520(f) of the act, providing FDA with the authority to add preproduction design controls to the CGMP regulation. This change in law was based on findings that a significant proportion of device recalls were attributed to faulty design of product. The SMDA also added new section 803 to the act (21 U.S.C. 383) which, among other things, encourages FDA to work with foreign countries toward mutual recognition of CGMP requirements. FDA undertook the revision of the CGMP regulation to add the design controls authorized by the SMDA to the CGMP regulation and because the agency believed that it would be beneficial to the public and the medical device industry for the CGMP regulation to be consistent, to the extent possible, with the requirements for quality systems contained in applicable international standards. FDA published the revised CGMP requirements in the final rule entitled "Quality System Regulation" in the Federal Register of October 7, 1996 (61 FR 52602). This regulation became effective on June 1, 1997 and remains in effect.

B. THE MDR REGULATION

The first Medical Device Reporting (MDR) regulation became final on December 13, 1984. As a result of changes mandated by the Safe Medical Devices Act (SMDA) of 1990, and the Medical Device Amendments of 1992, the 1984 MDR regulations (21 CFR 803 & 807) were revised and published on December 11, 1995. The FDA Modernization Act of 1997 made additional changes and a revised MDR regulation was proposed in May 1998. The final revised MDR regulation was published in the Federal Register on January 26, 2000. The latest version of MDR regulation includes reporting requirements for manufacturers, user facilities, and importers. MDR reporting for medical device distributors (except importers) was revoked by the FDA Modernization Act of 1997. Distributors are, however, still required to maintain complaint records, per 21 CFR 803.18(d)(1-3).

21 CFR Part 803 requires manufacturers of medical devices, including in vitro diagnostic devices, to report to FDA whenever the manufacturer or importer receives or otherwise becomes aware of information that reasonably suggests that one of its marketed devices:

1. may have caused or contributed to a death or serious injury or,
2. has malfunctioned and the device, or any other device marketed by the manufacturer or importer, would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

NOTE: Importers (initial distributors) of medical devices are subject to 21 CFR Part 803 published in the Federal Register on January 26, 2000, and effective March 27, 2000.

C. THE MEDICAL DEVICE TRACKING REGULATION

Under the authority of section 519(e) of the Act, the agency may issue a written tracking “order” that tells a manufacturer to implement a tracking program that meets the requirements of 21 CFR Part 821. Devices subject to tracking may include those that are permanently implanted or life sustaining/life supporting devices that are used outside a device user facility. These devices are considered reasonably likely to cause serious adverse health consequences if they fail. The regulation is intended to ensure that, in the event of a recall or safety alert, a tracked device can be traced by the manufacturer from the device manufacturing facility to the end user or patient.

D. THE CORRECTIONS AND REMOVAL REGULATION

The Corrections and Removal regulation requires manufacturers and importers to report promptly to FDA any corrections or removals of devices being undertaken to reduce risk to health.

E. THE REGISTRATION AND LISTING REGULATION

The Registration and Listing regulation requires manufacturers and foreign exporters to register and list their devices; and importers to register. (See Part III)

PART II

IMPLEMENTATION

A. OBJECTIVES

QUALITY SYSTEM REGULATION

1. To identify domestic and foreign manufacturers who are not in compliance with the Quality System regulation. To bring such manufacturers into compliance through voluntary, administrative and/or regulatory means, as appropriate.

MEDICAL DEVICE REPORTING REGULATION

2. To identify manufacturers and importers who are not reporting information to FDA in compliance with the Medical Device Reporting (MDR) regulation. To bring such firms into compliance through voluntary, administrative and/or regulatory means, as appropriate.

MEDICAL DEVICE TRACKING REGULATION

3. To identify manufacturers and importers who are not in compliance with the Medical Device Tracking regulation. To bring such firms into compliance through voluntary, administrative and/or regulatory means, as appropriate.

CORRECTIONS AND REMOVALS REGULATION

4. To identify manufacturers and distributors who are not in compliance with the Corrections and Removals (CAR) regulation. To bring such firms into compliance through voluntary, administrative and/or regulatory means, as appropriate.

REGISTRATION AND LISTING REGULATION

5. To identify firms who are not in compliance with the Registration and Listing regulation. To bring such firms into compliance through voluntary, administrative and/or regulatory means, as appropriate.

B. PROGRAM MANAGEMENT INSTRUCTIONS

1. The following guidelines are suggested for implementing this compliance program:
 - a. This compliance program is to be used to conduct Quality System inspections of devices. The profile information should be updated in FACTS for QS inspections.

Instructions for updating firm profiles in FACTS are referenced in the IOM Exhibit 5-14, and on the Office of Enforcement's intranet.

- b. Many large firms have several manufacturing facilities located in more than one district. These firms often have a research and development (R&D) center or corporate design facility, which services several manufacturing facilities.
- Upon completing an inspection of an R&D center or corporate design facility, districts should send copies of the inspection report to the home districts of the firm's manufacturing facilities
 - Unless additional information must be obtained from the manufacturing facility, the home district of the manufacturing facility during the next inspection need only verify the coordination aspects of the design control activities as long as the inspection of the R&D center or corporate design facility was conducted within the previous two years. Examples of design control coordination activities are:
 - How design change information is shared, verified, and, where appropriate, validated as full scale manufacturing;
 - How design transfer activities at the manufacturing facility are verified;
 - How the risk analysis is performed with respect to manufacturing controls; and,
 - How the risk analysis is continually being updated as manufacturing changes occur.
 - Likewise, if an inspection of the R&D center or corporate design facility has not been conducted within the previous two years, the home district of the manufacturing facility should issue an assignment to the home district of the R&D center or corporate design facility requesting a design control inspection. The above guidance is NOT applicable to Pre-Approval inspections.
- c. Sterilization of medical devices is covered as a part of the QSIT inspection under this compliance program. Guidance provided in the QSIT Guide is to be followed when inspecting sterilization processes for the following types of facilities:
- device manufacturers that sterilize their own product
 - device manufacturers that use contract sterilizers
 - contract sterilizers

Medical Devices related to AIDS diagnosis and screening, blood banking, blood screening and/or human blood processing will be inspected under this compliance program and CBER's compliance program 7342.008, "Inspection of Licensed Viral Marker Test Kits." For guidance, see the Intercenter Agreement between the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health, dated October 31, 1991.

The Biologics and Devices Intercenter Agreement can be found at the following web site:
<http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121175.htm>

2. Scheduling Inspections of Medical Device Manufacturers

a. Priorities for QS Inspections

Districts should target coverage of manufacturers of Class II and Class III devices utilizing a risk based methodology. Resources must be directed towards accomplishing performance goals.

Selection of firms to accomplish the performance goals and then remaining work plan obligations should be focused using the risk based model below:

- 1) Pre-Market and Pre-Clearance inspections under MDUFMA (Inspections of manufacturers of devices with a pending PMA approval will be assigned under the PMA Compliance Program 7383.001)
- 2) Manufacturers of Class III devices that have never been inspected
- 3) Compliance Follow Up/For Cause Inspections (See Part III B for further discussion)
- 4) Manufacturers of high risk devices which can be identified by:
 - A. Special Assignment from CDRH;
 - B. Devices with a higher frequency of recalls and MDRs;
 - C. Devices that are driven by software and those with rapidly evolving technological changes. Both of these types of devices are subject to rapid and potentially poorly controlled modifications that could affect their continued safety and efficacy; or,
 - D. New devices that have not been manufactured and distributed for very long.
- 5) Single Use Device Reprocessors: Hospital reprocessors and third party reprocessors. See Part III of this program for further instructions related to reprocessors.

Highest priority should be given to MDUFMA assignments and those Class III device manufacturers that have not been previously inspected. The high risk device category noted in 4) above, lists suggestions to the field on how to identify firms for surveillance inspections based on a risk model.

b. Class I Device Manufacturers

All Class I devices, including those exempted from most of the Quality System regulation requirements, must comply with record keeping requirements and complaint file requirements, as well as reporting requirements under the MDR regulation. Class I manufacturers should not be routinely scheduled for inspection but should receive lowest inspectional priority unless addressed by a special, "For Cause" assignment or when a health hazard is apparent. Use the following link to determine if a device is Class I exempt from QS requirements:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm>

If inspecting a manufacturer that was originally planned as a Class I QS non-exempt, Class II or III device firm, and the inspection finds that the firm no longer makes Class I QS non-exempt, Class II or Class III devices, the investigator should review the firm's complaint handling system and MDR practices and then terminate the inspection. The district should report the time against PAC 82845A.

3. Pre-Announcement of Inspections

Refer to Guide to Inspections of Quality Systems, August 1999, and IOM 5.2.1, Pre-Inspectional Activities.

4. Annotation of the FDA 483

Annotation of the FDA 483 should occur for all medical device inspections unless the manufacturer declines. Refer to IOM 5.2.3.4.

5. Resource Instructions

Only QSIT trained individuals should perform these inspections. Contact DDFI (HFC-130) should the need for expertise, not otherwise available in the Region, become apparent (Refer to FMD No. 142). When possible, Electro-Optical Specialists (EOS) should be used for inspection of laser devices, whose time is reported under PAC 86001. If QSIT trained, EOS's should also conduct the QS portion of this program.

PART III

INSPECTIONAL

BACKGROUND

This program includes guidance for determining compliance with the Quality System (QS) regulation, Medical Device Reporting (MDR) regulation, Medical Device Tracking regulation, Corrections and Removals regulation, and the Registration and Listing regulation.

A. OPERATIONS

1. Inspectional Strategy

The QS inspectional goal is to assess the firm's quality management system for compliance with the appropriate regulations. The QS inspection should generally start with a walk through of the facility to become familiar with the firm's operations and general state of control. See IOM 5.1.2.2.

The inspection will assess the firm's systems, methods, and procedures to ensure that the firm's quality management system is effectively established (defined, documented and implemented) and effectively maintained. QS inspections should include the assessment of post-market information on distributed devices to include:

- Review of recalls
- Review of MDRs (Be alert to the fact that MDRs may contain information on recalls that have not been reported through the district under 21 CFR Part 806.)
- Review of corrections and removals
- Review of significant changes in device specifications or in the manufacturing specifications
- Follow-up on previous FDA 483 observation(s), to include the corrections, corrective actions or preventive actions for the observation(s) and the related system(s)

Available post-market information should be reviewed as a part of the preparation for the inspection, in order to facilitate efficient time spent at the facility. Identify in the EIR post-market information reviewed during the inspection, and adequately document your findings. See IOM 5.10.4.3.9. Any problems identified as a result of the review of post-market information should be developed during the inspection.

IMPORTANT NOTE: The review of post-market information does not mean that the investigator should open the inspection with the review of complaints and complaint information. Complaints should be reviewed within the context of the Corrective and Preventive Action sub-system according to the procedures described below in this part.

a. QS Inspections

QS inspections should generally be conducted using the Quality System Inspection Technique (QSIT). Guidance for performing an inspection is provided in the Guide to Inspections of Quality Systems, August 1999, also called the QSIT Guide [<http://www.fda.gov/downloads/ICECI/Inspections/UCM142981.pdf>]. This QSIT tool can be scaled to meet the needs of each particular inspection. The table below correlates the level of inspection and the guidance on how to perform the inspections.

TABLE

Inspection Level	Type of Inspection	Guide to Inspections
1	Abbreviated	QSIT – Two subsystems; Corrective and Preventive Actions (CAPA) plus Production and Process Controls (P&PC) or Design Controls (PAC 82845A)
2	Comprehensive	QSIT - The four major subsystems; Management Controls, Design Controls, CAPA and P&PC (PAC 82845B or 82845P or 82A800)
3	Compliance Follow-up*	As directed by inspectional guidance and elements of QSIT (PAC 82845C)
Special	For Cause*	As directed by inspectional guidance and elements of QSIT (PAC 82845G)
Special	Risk Based Work Plan	As directed by CDRH inspection assignment and elements of QSIT (PAC 82845H)

- * Compliance Follow-up, For Cause, and Risk Based Work Plan inspections are dictated by the previous FDA 483 findings and other regulatory information and may differ from the typical QSIT approach. The inspectional guidance provided by the assignment, the district compliance branch, and/or CDRH will guide the direction of these inspections. However, elements of the QSIT Guide may also be utilized. See further details below.

Investigators must ensure that the EIR clearly states what was covered during the inspection due to the directed nature of these types of inspections.

NOTE: The Quality System regulation can be grouped into seven subsystems; however, the following four subsystems are considered major subsystems and are the basic foundation of a firm's quality management system: Management Controls, Design Controls, Corrective and Preventive Actions (CAPA), and Production and Process Controls (P&PC). MDR, Corrections and Removals, and Tracking requirements (where applicable) should be covered when covering the CAPA subsystem. The three remaining subsystems (Facilities and Equipment Controls, Materials Controls and Document/Records/Change Controls) cut across a firm's quality management system and are evaluated while covering the four major subsystems.

In the work plan, Level 1 Abbreviated (82845A), Level 2 Comprehensive (82845B), Level 3 Compliance Follow-Up (82845C), For Cause (82845G), Risk Based Work Plan (82845H) and Accredited Persons (82845P or 82A800) inspections are planned for each district. Planning resources for these five PACs provides greater control at the district level on the type of inspection conducted to maximize resource utilization and provide the flexibility needed to insure the Performance Goals are met. In utilizing this flexibility, districts must continue to monitor their accomplishments to assure that the Performance Goals and work plan are met.

b. Level 1 Inspections - PAC 82845A

Level 1 inspections are Abbreviated Inspections.

This level of inspection (CAPA plus P&PC or Design Controls) may be used for routine surveillance and initial inspections of all firms, other than firms that manufacture Class III devices. However, it is recommended that initial inspections of Class II manufacturers utilize a Level 2 Comprehensive inspection whenever district resources permit. Level 1 inspections should cover the CAPA subsystem, then P&PC or Design Controls, using the QSIT Guide. The selection of CAPA plus either the P&PC or Design Controls subsystem will provide an adequate review of the compliance status of the firm.

The following should be considered in determining whether to select P&PC or Design Controls:

- CAPA findings during the inspection
- Subsystems covered during the previous EI. The previous EIR(s) should be reviewed to determine which subsystems were previously covered. The selection of the P&PC or Design Controls subsystem should be alternated over time so that more subsystems within a firm's overall quality management system are assessed
- Significant changes since the previous EI. Determine if there were any design changes which required a new submission or application, or if there were any major

- process changes
- Post market information indicating potential design problems.

The EIR must clearly state which subsystem, P&PC or Design Controls, was chosen and why.

Note: The adequacy of the correction(s), corrective action(s) or preventive action(s) related to any FDA 483 item(s) from the previous inspection should be covered, even if the entire subsystem will not be reviewed during the current Level 1 inspection.

c. Level 2 Inspections - PAC 82845B or 82845P

Level 2 inspections are Comprehensive Inspections.

Level 2 inspections will cover all four major subsystems (Management Controls, Design Controls, CAPA, and P&PC) as explained in the QSIT Guide. The Level 2 inspection is considered a comprehensive review of the compliance status of the firm.

Level 2 inspections will be performed:

- For all initial inspections of Class III device manufacturers and, where possible, Class II device manufacturers
- By assignment
- For foreign inspections
- For training
- For Accredited Persons audits (PAC 82845P)
- When an inspection, which started out as Level 1, reveals post market information and/or objectionable conditions which cannot be adequately assessed as a Level 1 inspection. (Before converting to this more comprehensive level, district management should be informed.)
- Where district work plan resources permit (Level 2 should be considered for any inspections of Class II and Class III device manufacturers. The decision to use Level 2 inspections should be based on risk.)

Note: For more information on the Accredited Person audits see “Accredited Person Inspection Program (Medical Devices) Performance Audit Procedures” on the Division of Human Resource Development’s (DHRD’s) intranet website under the certification/related programs/accredited person program section.

The Level 2 QSIT approach was validated using the following inspectional sequence: Management Controls, Design Controls, CAPA and P&PC. This inspectional sequence allows the investigator to review design control issues and how the device specifications were established before reviewing the CAPA subsystem. Investigators may, however, start with Management Controls, followed by CAPA, Design Controls, and P&PC with

appropriate linkages. Information from Design Controls and CAPA may be used to select the products and processes for inspecting production and process controls, and appropriate linkages. The subsystems may be inspected in any appropriate and justifiable sequence in order to perform a timely and effective inspection.

Selection of manufacturing processes for inspectional coverage should include the following considerations:

- CAPA indicators of process problems
- Processes used to manufacture high risk products
- Processes that have a high risk of causing product failure
- Processes that require process validation
- Processes that are new to the manufacturer
- Processes that cover a variety of process technologies and profile classes
- Common processes used in multiple products
- Processes not covered during previous inspections

It is important to thoroughly cover Purchasing Controls, to include outsourced processes, as a QSIT linkage under P&PC whenever P & PC is covered. The Purchasing Control coverage must be documented in the EIR, especially if the manufacturer contracts a sterilization process or contracts the manufacture of significant components, subassemblies, or processes.

d. Level 3 Inspections - PAC 82845C

Level 3 inspections are Compliance Follow-up Inspections.

Level 3 inspections are necessary after a firm is found to have Situation I conditions during a previous QS inspection which was classified Official Action Indicated (OAI). (See Part V of this compliance program for information on Situation I and OAI.) Level 3 inspections will also be performed when directed by assignment.

The QSIT Guide should be used for guidance, but the inspectional guidance provided by the assignment, the district compliance branch, and/or CDRH will guide the flow of the inspection. The district compliance officers should be contacted during Level 3 inspections to assure that:

- Appropriate inspectional areas are covered with enough depth to support any findings
- Noncompliant findings (conditions) are adequately developed and documented
- Sufficient evidence is collected to support an appropriate regulatory action recommendation

Note: Foreign inspections, as discussed below, are Level 2 inspections and, therefore,

the option to stop an inspection in the next two diagrams does not apply.

If the previous inspection was a Level 2 inspection:

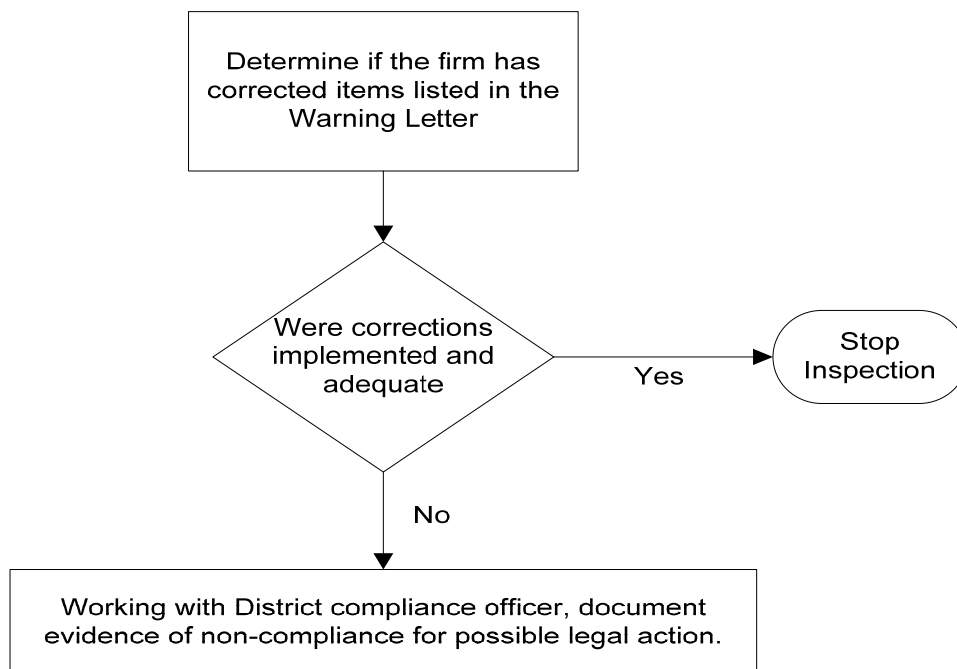
During domestic Level 3 inspections:

(A) Verify that adequate correction(s) and corrective action(s) have been implemented to the quality system problems previously identified.

(B) If the correction(s) and corrective action(s) were not implemented or were not implemented effectively, verify that the deficiencies continue to exist and provide adequate evidence to support a possible regulatory action.

(C) Document any additional quality system problems observed during the inspection, and provide adequate evidence to support a possible regulatory action.

The chart below describes the steps for the Level 3 domestic inspection after a Level 2 inspection.



If the previous inspection was a Level 1 inspection:

When the previous inspection was performed as a Level 1 inspection, the other two major subsystems previously not covered must be covered in addition to the inspectional

guidance. It is important that the combination of the Level 1 and Level 3 inspections cover all four of the major subsystems in order to ensure a comprehensive review of the firm's quality management system.

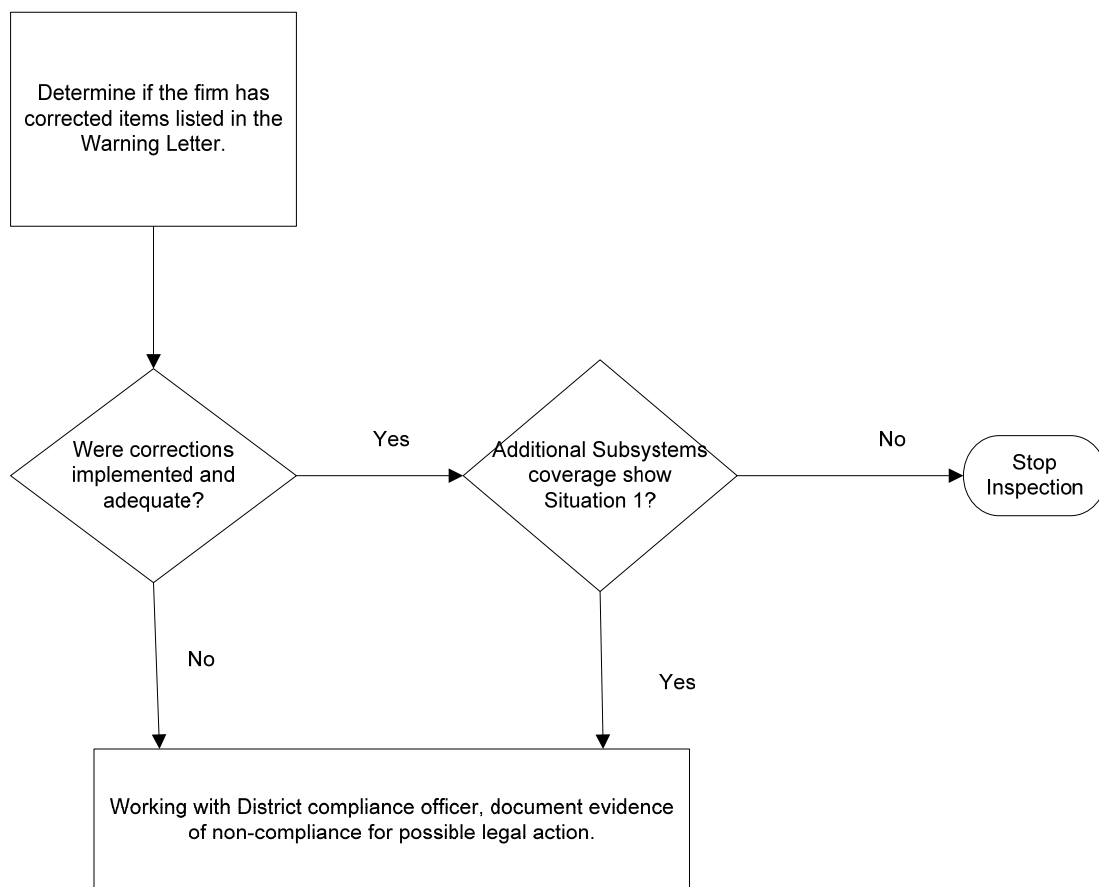
During domestic Level 3 inspections:

(A) Verify that adequate correction(s) and corrective action(s) have been implemented to the quality system problems previously identified; and

(B) If the correction(s) and corrective action(s) were not implemented or were not implemented effectively, verify that the deficiencies continue to exist and provide adequate evidence to support a possible regulatory action.

(C) Document any additional quality system problems observed during the inspection, and provide adequate evidence to support a possible regulatory action.

The chart below describes the steps for the Level 3 domestic inspection after a Level 1 inspection.



e. For Cause Inspections - PAC 82845G

For Cause inspections are carried out in response to specific information that raises questions, concerns, or problems associated with a FDA regulated firm or commodity. This information could come to the attention of FDA from any source and including, but not limited to, the following:

- Results of a sample analysis
- Observations made during prior inspections
- Recall or market withdrawal
- Consumer or employee complaint
- Adverse reaction report
- Suspicion of fraud

For Cause inspections are usually initiated at the request of CDRH, ORA headquarters, Regional or District directives. For Cause inspections are dictated by the source of information and may differ from the typical QSIT approach. These inspections are generally more in-depth in particular areas than typical QSIT inspections. The inspectional guidance provided by the assignment, the district compliance branch, and/or CDRH will guide the flow of these inspections, however, elements of the QSIT Guide may also be utilized.

For Cause inspections should be directed towards the quality problem(s) and, if applicable, trace the underlying cause, assuring that appropriate correction(s) and corrective action(s) are initiated.

If a serious public health risk is encountered during a QSIT inspection, consideration should be given to performing a For Cause inspection. The district compliance branch should be consulted prior to this decision.

For Cause inspections may also be initiated at a contract sterilizer when an inspection at a device manufacturer raises questions about the adequacy of processing or quality assurance by the contract sterilizer. Likewise, an inspection at a contract sterilizer may lead to a For Cause inspection of device manufacturers if significant deficiencies are observed. The deficiencies may be an indication that the device manufacturer(s) has not assumed appropriate responsibility for the sterilization validation and processing of its own devices. The district that has identified the need for the additional coverage is to notify the home district of the establishment that needs a For Cause inspection.

f. Risk Based Work Plan Inspections - PAC 82845H

The risk based work plan inspection program was developed to focus limited resources on key public health needs. It reflects the broader goals of the Center and Agency to utilize science-based risk management in the selection and prioritization of sites for inspection. This provides the most health promotion and protection to the public at the

least cost by focusing on medical devices and firms which pose the greatest risk.

Data collected throughout the total product life cycle (e.g. premarket submissions, recalls, adverse event reports) is analyzed to detect risks posed by medical devices. The beneficial public health impact of the devices and the potential risks of device failure are also considered. In general, the project's objectives include the following:

- a more consistent, rigorous, science-based approach to selection of sites for inspection
- increased transparency and rigor in decision making
- employment of limited resources towards sites that pose the potentially greatest risk to public health

Risk based work plan inspections are initiated at the request of CDRH. These inspections are focused by the Center's analysis and work plan assignment and may differ from the typical QSIT approach. These inspections are generally more in-depth in particular areas than typical QSIT inspections. The inspectional guidance provided by the assignment will guide the flow of these inspections; however, elements of the QSIT Guide may also be utilized.

If a serious public health risk is encountered during a risk based work plan inspection, CDRH and the district compliance branch should be consulted.

g. Foreign Inspections

All foreign inspections should be conducted using the QSIT Guide under the Level 2 strategy, and any special instructions contained in the inspection assignment. The foreign manufacturer's compliance with registration and listing requirements should be covered during foreign inspections. The failure of foreign device manufacturers to list products exported to the US will subject medical devices to detention upon entry.

Foreign inspections are subject to time constraints but need to follow the instructions for a Level 2 inspection as described above. Requests for documents should be made as early as possible to give the firm time for written or oral translations and obtaining documents that may be located in US offices. Oral translations need to be documented in the EIR if that information is utilized in supporting an observation(s).

2. Inspectional Instructions

a. Required Statement(s)

The following statement should be included on each FDA 483:

This document lists observations made by the FDA representative(s) during the

inspection of your facility. They are inspectional observations and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective actions in response to an observation, you may discuss the objection or action with FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

For all medical device inspections the FDA 483 should contain the following additional statement:

The observations noted in this form FDA 483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self audits to identify and correct any and all violations of the quality system requirements.

b. Satellite Program Areas

Some program areas are considered satellites to the four major quality management system subsystems (Management Controls, Design Controls, CAPA, and P&PC):

CAPA Satellites:

- MDR
- Corrections & Removals
- Tracking

Production & Process Control Satellite

- Sterilization

Refer to the QSIT Guide for details on how to inspect those areas mentioned above. Refer to Part V of this Compliance Program for guidance on Regulatory and Administrative follow-up to these programs. Report the time spent on the Satellites under the appropriate corresponding PAC. Time for coverage of these satellites is averaged into the Level 1 and Level 2 inspectional work plan modules.

The following guidance should be used for determining when to cover the various programs.

QS should be covered during each inspection. Coverage is determined by the "level" of desired inspection. See Part III, above for guidance on which level to use and which subsystems to inspect.

MDR compliance should be covered during each inspection. Prior to initiating an inspection, the MDR data should be reviewed using eCIRS or by going to CDRH to

obtain information regarding the firm's current reports. Be alert to the fact that MDRs may contain information on recalls that have not been reported through the district under 21 CFR Part 806.

Corrections & Removals. Determine during all QS inspections whether the firm has initiated any corrections or removals since the previous inspection, and inspect for compliance with the Corrections & Removals regulation as described in the QSIT Guide. A Corrections & Removals inspection should also be initiated when a manufacturer is reporting corrections or removals in MDR reports or Part 806 reports. Be alert to the fact that MDRs may contain information on recalls that have not been reported through the district under 21 CFR Part 806.

Tracking. A tracking inspection is recommended for devices that were issued a tracking order, each time CAPA is covered. To obtain Tracking information, refer to "Medical Device Tracking Guidance for Industry and FDA Staff" dated May 5, 2003, or access <http://www.fda.gov/cdrh/comp/guidance/169.html>.

Sterilization. When the P & PC subsystem is being inspected, sterilization should be chosen if not covered during the previous inspection unless:

- CAPA indicators of existing or potential problems are found with any other specific process or,
- Other higher risk processes exist.

c. Sampling Records

The QSIT Guide includes instructions for sampling records for review. Sampling is an important tool for reducing the time spent reviewing records while being able to make statistically based inferences about the significance of the findings. The QSIT sampling table should be used for sampling records for evaluating the firm's adherence to requirements and their procedures, not for performing data verification or analysis.

During Level 1 and 2 inspections, the review of the records may be terminated if objectionable conditions are observed before the entire sample is reviewed. An FDA 483 observation may be made that the objectionable condition was found, and then move to the next part of the inspection. However, QSIT Guide instructions caution that not reviewing the entire sample may result in the loss of additional information which may be useful in understanding the potential prevalence of the objectionable condition, or the failure to identify other objectionable conditions.

During Level 3 inspections, however, the investigator and the compliance officer should work together closely to plan how sampling will be conducted. It is important for the compliance officer to be confident that the level of sampling will be sufficient to document the deficiency and support a potential regulatory action. During Level 3

inspections, it is recommended that the investigator review the entire sample of records to provide a complete picture of any deficiencies identified during sampling.

When evidence is collected utilizing the sampling tables, the EIR should reflect the following information:

- The type of records reviewed
- The sampling table used, Table 1 or 2
- The row used, row A, B, C, D, E or F
- The size of the sample and the number of records it was based on
- The number of records actually reviewed (may be the same as or different from the size of the sample)
- The results of sample review

Computer aided techniques may also be useful tools to efficiently evaluate electronic records (e.g. a large volume of complaint files) or accomplish assignment specific objectives (e.g., evaluating for trends in product specific complaint or failure data).

Note: Statistical support is available from CDRH, Office of Surveillance and Biometrics. DFI experts are available to assist with support in applying computer aided techniques.

3. **Special Instructions Concerning Design Controls**

The inspectional authority for review of design control records is derived from Section 704(e) of the Act. Such authority applies only after the establishment has manufactured the device for which the design has been under development or taken an action that precludes the argument that the product under development is not a device. Such action includes: (1) submitting to an Institutional Review Board plans for clinical investigation of the device, (2) submitting to FDA a Product Development Protocol (PDP), (3) submitting to FDA an IDE, 510(k), PMA, Humanitarian Device Exemption (HDE) or Premarket Report (PMR), and (4) changes to an already marketed device. Therefore, FDA has inspectional authority to review design control records when the device has been placed on the market or when any of the four actions above have occurred.

The above limitation does not apply to inspectional authority to review all generic design control procedures at any point in time.

Review of design controls should cover any design processes performed after June 1, 1997. The manufacturer is not required to retrospectively apply design controls to any stages in the design process that it had completed prior to June 1, 1997, unless changes have been made to the design (including changes in ownership or where the designed device will be manufactured) after June 1, 1997.

If a manufacturer normally designs its own devices, but has not initiated any design changes to current devices since June 1, 1997, or does not have a design project

underway that is reviewable by FDA given the limitation discussed above, investigators should limit their coverage to a review of the design change control procedures that the manufacturer must have defined and documented.

There are a number of multi-establishment firms that conduct all design activities at a single facility (sometimes referred to as a research and development (R&D) center or corporate design facility). If the establishment scheduled for inspection is serviced by an R&D center or corporate facility, review the establishment jacket before beginning the inspection, consult the agency's on-line OEI databases, and/or directly contact the district involved. Determine if the home district of the R&D center or corporate design facility has conducted a design control inspection of that facility within the previous two years. If such an inspection was conducted, it will not be necessary to conduct a design control assessment at the establishment scheduled for inspection. If an inspection was not conducted within the previous two years, issue an assignment to the home district of the R&D center or corporate design facility requesting a design control inspection.

Some manufacturers have their devices designed under contract. These manufacturers must comply with the requirements for using contractors or service suppliers under 21 CFR § 820.50 as well as ensuring compliance with 21 CFR § 820.30. The manufacturer must maintain or have reasonable accessibility to copies of a Design History File for any device that is in production.

Observations relating to Design Controls placed on the FDA 483 should be limited to the adequacy of, and adherence to, the procedures and/or controls established by the firm. **Do not place observations on the FDA 483 that concern the adequacy, safety, or efficacy of a particular design.** Any such concerns should be noted in the EIR and flagged for review by the Office of Device Evaluation or the Office of In Vitro Diagnostic Devices/CDRH.

4. Special Instructions for Sterilization Processes

Sterilization Process Controls section found in the QSIT Guide is a sub-part of the Production and Process Controls subsystem. The instructions for inspecting sterilization processes are applicable at the following types of facilities:

- device manufacturers that sterilize their own product
- device manufacturers that use contract sterilizers
- contract sterilizers

NOTE: The portion of the inspection spent covering sterilization processes should be reported under PAC 82845S.

Refer to Part III, A. 6, for guidance on collection of samples relating to sterilization issues.

5. **Inspection of Radiation Emitting Devices**

Medical Devices which are also deemed to be “electronic products” as defined by the Federal Food Drug and Cosmetic Act, Subchapter C – Electronic Product Radiation Control, section 531(2), may be inspected under this compliance program. These devices have additional Radiological Health requirements to protect the public from unnecessary radiation. The requirements include the affixing of certification labeling, additional reporting and record keeping, and the continued testing to verify product conformance with applicable Federal Performance Standards promulgated under 21 CFR 1020 - 1050. If the device being inspected is subject to Radiological Health requirements, follow the appropriate Compliance Program. Report any Radiological Health time under the appropriate Radiological Health PAC.

When conducting QS inspections, a firm may manufacture medical devices which are capable of emitting electronic product radiation. Based on district concurrence, the firm’s devices should also be assessed against the applicable standards promulgated under Chapter V, Subchapter C - Electronic Product Radiation Control of the FD&C Act. This assessment is not a QS activity and should not be reported as a QS activity.

Use Compliance Programs 7386.001, 7386.002; and 7386.004 through 7386.007 for guidance on inspections in this area. For Field Compliance Testing of Diagnostic Medical X-Ray Equipment, use CP 7386.003.

Device manufacturers subject to existing FDA performance standards (21 CFR Parts 1020 – 1050) should include in their device master and history records those procedures and records demonstrating compliance with the applicable standard, self-certification (21 CFR 1010), and reporting (21CFR 1002 – 1005).

6. **Sample Collection**

For QS, MDR, Tracking, and Correction and Removals violations, samples are not generally necessary to support a Warning Letter. However, the District office may require, at least, a documentary sample to support even a Warning Letter. Follow the district requirements. Also refer to IOM Section 5.6.1.2.

Samples may be required to support further action beyond a Warning Letter. The investigator should work with District management and compliance branch on deciding to collect samples to support QS violations. Physical samples should not be routinely collected to support QS cases. If the district should reference violative documentary or physical samples as evidence to support QS deviations, the sample should be tied to the QS deviation to show a cause/effect relationship.

Normally, the collection of samples for sterility issues is not to be performed during Level 1 (Abbreviated) inspections of device manufacturers or contract sterilizers. If

sterility issues involve packaging or seam integrity, sample collection may be needed. The following items provide guidance on sampling decisions. For questions regarding sterilization issues or the need to collect samples related to the sterilization process, contact CDRH, Office of Compliance. Guidance on sampling decisions can be found in Part IV C.

- Finished device samples should **not** routinely be collected and tested for sterility to prove quality system deficiencies in sterilization validation or process control. Under certain circumstances, the Center may request that samples be collected for sterility testing.
- Field examination of packaging used for sterile devices may be indicated when the assessment of packaging operations demonstrates a lack of control such that inadequate packaging is likely to occur. Examine the packages for integrity of the sterility barrier, paying close attention to seals.
- Samples of defective packaging found during a visual field examination, if regulatory action is contemplated for packaging deficiencies, consist of 20 sterilized packaged devices.
- Bioburden samples are to be collected **only** 1) when the review of the results of bioburden testing performed by the manufacturer finds unrealistically low results; and, 2) the sterilization process is a bioburden based cycle with no safety overkill element. The sample should consist of 20 unsterilized devices.
- Biological indicators are **not** to be collected routinely. Collect 40 biological indicators only if there is reason to question the effectiveness of the indicators or under direction by the Center.
- Endotoxin samples are to be collected **only** when endotoxin control is necessary for the device and when the review of the manufacturer's test methodology suggests that the manufacturer's test results may be unrealistically low. Collect 10 sterilized devices.

If the investigator is uncertain as to whether a sample should be collected, he/she should consult with district management who may consult with the CDRH Headquarters Laboratory Liaison, WEAC, or the Division of Field Science in ORA on the laboratory capability to conduct the analysis. (See Part VI, B. for program contacts)

B. ADDITIONAL CONSIDERATIONS

1. Registration and Listing

Registration and Listing should be reviewed as part of the pre-inspectional activities and evaluated during inspections. Inspections should be limited to the minimum time and

effort it takes to make an assessment. Review of a random sample of device listings (less than six) and the most recent registration is adequate. Also, randomly select two products from the firm's catalog (or equivalent document), and determine whether listing was done. Assess whether these documents are up to date and correct.

NOTE: Registration and Listing should be covered during both domestic and foreign inspections. Per IOM section 5.2.3.3, do not place the violative findings for registration and listing on the FDA 483, but make verbal statements to the top management about the concerns at the close-out discussion. See Part V, Section E for regulatory considerations.

For specific guidance concerning device registration and listing requirements see IOM Subchapter 2.9 – Regulatory Submissions, section 2.9.2.1 Device Registration and Listing. See Exhibit 5-12 for a Summary Registration and Listing requirements for medical devices.

2. **Imports**

No import field examinations or sample collections are scheduled under this program.

3. **Exports**

The FDA Export Reform and Enhancement Act of 1996 amended Section 802 of the FD&C Act to allow an establishment to export unapproved Class III devices or Class II devices not cleared and subject to mandatory standards under Section 514, to any of those countries listed in Section 802 of the Act that authorize marketing, and to any other country that recognizes the marketing authorization of a listed country without first obtaining FDA authorization. Section 802 also requires that any such device must be manufactured in "substantial conformity with current good manufacturing practice requirements."

Section 801(e)(1) of the Act permits the importation of adulterated or misbranded devices, components, or accessories for further processing or incorporation into a finished device, provided that the device is subsequently exported and not sold or offered for sale in domestic commerce.

Chapter 9 of the Regulatory Procedures Manual and IOM Section 6.1.2 provide guidance on "import for export", including record keeping requirements and the types of operations that qualify as further processing or incorporation of a component into a finished device. Exports under section 802 are subject to cGMP requirements found in the QS regulation.

Manufacturers are encouraged to make prior arrangements with their FDA district office before initiating an import for export operation. The review of the factory jacket should reveal when firms are performing such operations. The inspection should confirm that the firm is complying with the applicable requirements of the QS regulation for exports under section 802.

4. **Electronic Records and Electronic Signatures**

Follow agency policy when inspecting electronic records and signatures, see Part VI.

C. REMARKETED DEVICES

1. **Remanufacturers of Used Devices**

Remanufacturers are persons who process, condition, renovate, repack, restore or do any other act to a finished device that significantly changes the finished device's performance or safety specifications or intended use [21 CFR 820.3(w)].

Remanufacturers are considered to be manufacturers, and are subject to all applicable requirements of the Quality System regulation, MDR requirements, Device Tracking requirements, Registration and Listing, and premarket approval or clearance requirements. If an establishment disputes its regulatory status, the district should refer the EIR to the appropriate Division of Enforcement within CDRH/OC for assistance in interpreting the definition of a remanufacturer.

NOTE: For a discussion of the above issues see Federal Register Notice: December 23, 1997 (Volume 62, Number 246), pages 67011 – 67013.

2. **Third Party Refurbishers/Reconditioners/Service of Used Devices**

Third party refurbishers, reconditioners, servicers and "as is" resellers of used devices are currently not subject to the requirements of the Quality System regulation. If the district receives an assignment to inspect such an establishment, the district should contact the Office of Compliance, Office of the Director, to determine the current regulatory status of such establishments.

3. **Reprocessors of Single Use Devices**

Third party reproducers of single use devices are considered to be manufacturers and are subject to those requirements of the Quality System regulation that apply to the operations they perform. See Enforcement Priorities for Single-Use Devices Reprocessed by Third Parties and Hospitals, August 14, 2000, for guidance on FDA's enforcement strategy at the following link:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM107164>

The district should contact CDRH, Office of Compliance, Office of the Director, for guidance before conducting an inspection of an establishment believed to be a third party reproducer of single use devices, when not part of the assignment.

4. Hospital Reprocessors

Hospital reprocessors are to be only inspected under CDRH assignment.

D. REPORTING

1. General Reporting requirements are listed on the cover page. Refer to the IOM for EIR formats. Always include device, device class, and subsystems covered in the EIR.
2. QS Observations--If there are observed violations of the QS requirements, place them on the Form FDA-483. The QSIT Guide provides guidance concerning major QS requirements and the identification of major deviations. The most serious system deficiencies should be noted on the Form FDA-483 first, then by subsystems if possible. Special Note: Refer to the IOM for information concerning annotation of the Form FDA-483.
3. 510(k) or PMA Observations--If the establishment does not have a valid:
 - PMA for a device that is offered for introduction into interstate commerce;
 - 510(k) for a device that was offered for introduction into interstate commerce for the first time after May 28, 1976; or,
 - Has made significant changes to a device that require a new 510(k), or PMA supplement,

then investigators should not place the observations on the Form FDA-483 unless concurrence is obtained from CDRH/OC and/or OIVD. When Center concurrence cannot be obtained before the inspection is completed, investigators are requested to obtain complete documentation and submit that documentation for CDRH review through the district compliance branch.

4. Registration and Listing Observations -- If a firm has failed to list device(s), or to verify that their listings are up-to-date every six months and update them if they are not, as required by 21 CFR Part 807, make note of this observation(s) in the EIR for consideration for action by the district Compliance Officer. If a firm has failed to renew its annual registration for the last two or more years as required by 21 CFR Part 807, make note of this observation in the EIR for consideration for action by the district Compliance Officer. All registration and listing observations should be reported to firm management.

NOTE: A firm's registration and listing status can be determined by querying the CDRH Public Registration and Listing database or by using the canned reports in the DRLM Universe in Business Objects.

Field Accomplishments and Compliance Tracking System (FACTS)--Refer to existing policy in the IOM.

5. FDA Field Accomplishments and Compliance Tracking System (FACTS)

- a. When selecting specific manufacturing processes to represent profile classes, investigators should give preference to:

- CAPA indicators of process problems
- Process used to manufacture high risk products
- Processes that have a high risk of causing product failure
- Processes that require process validation
- Processes that are new to the manufacturer
- Processes that cover a variety of process technologies and profile classes
- Common process used in multiple products
- Processes not covered during previous inspections

NOTE: If all profile classes are not directly covered during an inspection, but are covered indirectly under CAPA, then all profile classes the firm is involved with can be listed on the appropriate FACTS screen.

- b. Quality System Inspections conducted should include:
- (1) coverage of the device(s) specified in the assignment, or devices and related manufacturing processes representing all the same profile classes as the assigned device; and,
 - (2) other devices as required to provide coverage of any remaining profile classes, except QS exempt Class I devices.
- c. Since the QSIT approach covers systems, the findings from the inspection can apply to all profile classes at the firm.

PART IV

ANALYTICAL

A. ANALYZING LABORATORIES

The district will make all the necessary arrangements for proper handling of samples with the following designated testing facilities:

<u>TYPES OF DEVICES</u>	<u>ANALYZING LABORATORIES</u>
All General Medical Devices	Winchester Engineering and Analytical Center (WEAC) 109 Holton Street Winchester, Massachusetts 01890-1197
Radioimmunoassay	WEAC
All Other In Vitro Diagnostic Devices	Micro—WEAC Chem—WEAC
<u>Testing for sterility of finished devices, package integrity, bioburden, and endotoxins:</u>	WEAC
<u>Testing of biological indicators:</u>	WEAC

See PART VI regarding those persons designated as contacts for WEAC and specific products.

SPECIAL NOTE: For all other devices and questions concerning sampling of devices and laboratory capabilities, contact Division of Field Science (DFS), HFC-140.

B. ANALYSES TO BE CONDUCTED

Sample collection and analysis will be determined on a case-by-case basis through consideration of inspectional findings and compliance and scientific capabilities and expertise. Full collaboration between investigations and analytical personnel is essential. See Part III for additional information.

C. METHODOLOGY

1. Testing Finished Device Samples for Sterility

- a. Visually examine each unit to ascertain that its packaging is intact. Report all defects observed by describing the size, type and location of the defects. Units with defective packaging need not be examined for sterility.
- b. Finished device samples are to be tested in accordance with the requirements of current USP methodology for Sterility Tests. **Reference the FDA Sterility Analytical Manual for guidance on applying the USP methods.**
- c. Device samples are to consist of 60 units, as follows:

20 units tested in Soybean-Casein Digest Broth
 20 units tested in Fluid Thioglycollate Broth
 10 units for bacteriostasis/fungistasis testing
 2 units for system control
 8 units for method development
 60 units for re-test, if required under USP methodology

When 120 units are not available because of lot size or cost, follow the current USP recommendations for the minimum number of articles to be tested in each media, as follows:

<u>Number of Articles in the Batch</u>	<u>Number of Articles to be tested</u>
Not more than 100 articles	10% or 4 articles, whichever is greater
More than 100, but not more 500 articles	10 articles
More than 500 articles	2% or 20 articles, whichever is less

Note that the USP permits the division of articles into equal portions for addition to each of the specified media when the contents of the article are of sufficient quantity (see the current USP to determine what is a sufficient quantity).

NOTE: For the purposes of this compliance program, the “articles” referred to in the USP may be interpreted as devices.

d. Positive subsamples

Check cultures for growth daily, and begin qualitative analysis of growth immediately upon detection of growth. Follow subculturing procedures in the Sterility Analytical Manual. Continue to incubate growth vessels after subculture for full term analysis to detect slow growing bacteria and molds. For each subsample found to be non-sterile, prepare a pure culture of each contaminant. All isolates from sterility tests must be maintained until otherwise notified by CDRH or for one year.

2. Presterilization Microbial Contamination (Bioburden)

Bioburden testing is to be performed in accordance with the guidance provided in ISO 11737-1, Sterilization of medical devices - Microbiological methods - Part I: Estimation of population of microorganisms on products. The methodology used for estimating the bioburden must be validated. Twenty units are to be tested.

3. Analysis of Biological Indicators

Test 40 biological indicators according to current USP methodology using sterilization conditions specified on the indicator label. "Survival time and kill time" and "Resistance performance tests" are to be used. Eighty (80) additional biological indicators may be required if either performance test fails. Under some conditions, the D-Value may also be determined. That determination requires a minimum of 45 biological indicators. These determinations will be performed according to the claims of the manufacturer of the indicator or inoculated product. Pertinent test specifics will be required.

4. Analysis of Packaging Defects

Perform a visual, non-destructive, inspection of the package noting the existence and location of seal or material defects. Normally 20 packaged devices will be collected for analysis. Further testing may be performed using consensus standards such as those identified in the Part VI. A.1 references for the American Society for Testing and Materials (ASTM). Selection of the test will depend on the materials and construction of the package and on the nature of the noted or suspected problem.

5. Analysis of Endotoxins

Samples will be analyzed using the Bacterial Endotoxins Test found in the current USP and the Sterility Analytical Manual. Ten units are required for endotoxin testing.

6. Antimicrobial Effectiveness Testing

Samples will be analyzed using the Antimicrobial Effectiveness Test found in the current USP and the Sterility Analytical Manual. Ten units are required for testing.

PART V

REGULATORY/ADMINISTRATIVE FOLLOW-UP

A. QUALITY SYSTEM REGULATORY/ADMINISTRATIVE FOLLOW-UP

1. Compliance Decision

a. Situation I

The district has documented evidence indicating that one or more **major deficiencies** with the Quality System regulation have resulted in the inspection being classified as Official Action Indicated (OAI). Examples that may be considered include:

- Total failure to define, document, or implement a quality system or one of the seven subsystems. The following list only provides examples and is not all-inclusive:
 - No procedure(s) which address corrective and preventive actions.
 - No procedure(s) on how the quality data will be analyzed and utilized.
 - Where design controls are required, no design control procedure(s) for a particular device or family of devices, i.e., only high level design control procedures.
 - Where design controls are required, no design change control procedure(s).
 - No documented process validation for process(es) for which the results cannot be fully verified.
- A deficiency in one or more element(s) of the subsystems. The QSIT Guide focuses on the most important aspects within each subsystem and can be utilized to determine what the Agency believes is critical and therefore would constitute “major” problems if not adequately addressed. Particular attention should be paid to the relationships of requirements. For example, deficiencies in both purchasing controls and acceptance activities can indicate a major deficiency because control of components and suppliers depends on a mix of both of these activities, and if there are problems with one or both, assurances are greatly diminished.
- The existence of products which clearly do not comply with the manufacturer’s specifications and/or the Quality System regulation and which were not adequately addressed by the Corrective and Preventive Actions Subsystem (CAPA) program.

- Noncorrection or inadequate correction of **major deficiencies** from previous inspection(s). Repeat deficiencies of same or similar deficiencies from previous inspection(s).

If any major deficiencies exist, the district is expected to classify the EIR as OAI and, based on the significance (risk) of the device and the findings, the district should consider which administrative and/or regulatory action to initiate. Such actions include, but are not limited to, issuance of a Warning Letter, injunction, detention, seizure, civil penalty and/or prosecution. See Regulatory Procedures Manual for further guidance.

If any of these deficiencies exist for foreign manufacturers, based on the significance (risk) of the device and the findings, a Warning Letter and/or Warning Letter with Detention without Physical Examination will be considered by CDRH/OC.

IMPORTANT NOTE: If a serious health hazard is identified, and the firm is not cooperative in conducting a voluntary recall, an FDA mandated recall (Section 518(e) of the FD&C Act), administrative detention/seizure or injunction should be considered as the initial action to bring the situation under prompt control.

b. Situation II

The inspection documents QS deficiencies of a quantity and/or type to conclude that there is minimal probability, in light of the relationship between quality system deficiencies observed and the particular device and manufacturing processes involved, that the establishment will produce nonconforming and/or defective finished devices. The Form FDA-483, Inspectional Observations, will serve to inform the establishment of any objectionable findings.

IMPORTANT NOTE: A Situation II should not be assigned if the inspection documented major deficiencies and the firm responds only with promised corrections, corrective actions and preventive actions. In order for an inspection to be classified as Situation II, FDA must have documented evidence of effectively implemented corrections and corrective actions taken on any and all major deficiencies observed during the inspection.

2. Contract Sterilizers, Contract Device Manufacturers and Finished Device Manufacturers – Deciding Responsibility When Taking Regulatory Action

- a. The following is provided as guidance for deciding which party is to be held responsible when a finished device manufacturer uses a contract sterilizer to perform terminal sterilization on its devices or a contract device manufacturer:
- Contract sterilization and contract manufacturing are considered an extension of the finished device manufacturer's process. The finished device

manufacturer is ultimately responsible for assuring that validations, operations, process controls, quality assurance checks, etc. are appropriate, adequately documented and correctly performed.

- Contract sterilizers and contract manufacturers of finished devices are considered manufacturers for the purpose of applying the Quality System regulation in that they meet the definitions as described in 21 CFR § 820.3(l) finished device and 21 CFR § 820.3(o) manufacturer. Contract sterilizers and contract manufacturers of finished devices are subject to those parts of the Quality System regulation that apply to the operations that are performed.
 - The finished device manufacturer bears overall responsibility for the safety and effectiveness of the finished device and must control all contractors under 21 CFR § 820.50 Purchasing controls and 21 CFR § 820.80 Receiving, in-process, and finished device acceptance. However, a contract sterilizer/contract manufacturer of finished devices and the finished device manufacturer are all legally responsible for compliance with the Quality System regulation and for assuring the safety and effectiveness of the finished device.
 - Contract manufacturers, including contract testing or contract laboratories, that are not manufacturing a device meeting the definition of a finished device in 21 CFR § 820.3(l), are not required to meet the Quality System regulation. These contractors, even though they may meet the definition of a “manufacturer,” are controlled by the finished device manufacturer under 21 CFR § 820.50 Purchasing controls and 21 CFR § 820.80 Receiving, in-process, and finished device acceptance.
 - For contract sterilization, the written agreement between the manufacturer and contract sterilizer required by 21 CFR 801.150(e), may be referenced to determine how the parties have defined their respective responsibilities. For other contract manufacturers, any written agreements used as part of supplier controls under 21 CFR § 820.50, may be referenced to determine how the parties have defined their activities and respective responsibilities.
- b. When deviations are observed, proposed regulatory actions should reflect and identify the shared responsibilities between the contractor and finished device manufacturer. In some situations, it may be appropriate to initiate regulatory action against both the contractor and the device manufacturers:
- Appropriate action should be considered against the contract sterilizer or contract manufacturer of finished devices in areas for which it has the prime responsibility under any written agreement. It may be necessary to inspect more than one customer to develop supporting documentation to demonstrate the particular contractor does not appear to have adequate controls.

- When an inspection of a contractor finds violations in areas that are the responsibility of the finished device manufacturer (such as validation, biological indicators, package seal testing, etc.), these deviations are reported to the home district of the finished device manufacturer. Regulatory action consistent with the action of choice for the contractor should be considered for the finished device manufacturer.
- Because the finished device manufacturer is ultimately responsible for the safety and effectiveness of the device and, therefore, the contractor's activities, serious deficiencies found at a contractor's establishment will indicate consideration of regulatory action against the finished device manufacturer. Copies of Warning Letters issued to a contract sterilizer or contract manufacturer of finished devices should be sent to the finished device manufacturer with appropriate redaction. A copy should also be sent to the home FDA district office of the finished device manufacturer. These documents should be used as a basis for the next scheduled inspection of the finished device manufacturer.
- When a possible health hazard situation exists due to the contractor's operation; or an administrative or legal action is contemplated against a contract sterilizer or contract manufacturer of finished devices, the home FDA district office(s) of all finished device manufacturers utilizing that contractor should schedule an immediate follow-up inspection at all affected device manufacturers.

3. Violative Devices Sold to Government Agencies

It is agency policy to treat devices sold to the federal government in the same manner as devices sold to commercial accounts. Consequently, when FDA recommends against acceptance of a device by a government agency because that device, or its manufacturer, is in violation of the FD&C Act, FDA should also recommend appropriate regulatory/administrative action against the same or similar device sold to commercial accounts.

If an establishment has shipped a violative device to a Government agency, appropriate regulatory action consistent with the nature of the violation(s) may be taken even though there have been no shipments to commercial customers. Formal regulatory action in connection with a violative shipment may not be necessary in some cases. (For example, the establishment promptly corrects the violative condition, and the Agency would not require further action if the matter involved a device shipped to a non-government customer.) However, where corrections are not or cannot be made promptly, the main concern is preventing the subsequent shipment of the device to another customer. When the device has been shipped solely to a Government agency and is under control of that agency and there is no threat to the public, the ORA/Division of Compliance Information

and Quality Assurance (DCIQA) staff should ascertain the intention of the agency holding the goods (e.g., will they return or destroy the goods; will they request FDA to initiate seizure, etc.). If the procuring agency requests FDA action, ORA DCIQA staff will refer the matter to the home FDA district office for their consideration of an appropriate recommendation.

4. Administrative and Judicial Actions

Actions which may be considered include: FDA requested recall, FDA mandated recall, Warning Letter, seizure, injunction, prosecution, civil penalties and detention.

Corrections and corrective action proposals and documented evidence of those corrections and corrective actions should be submitted by a responsible official of the establishment in writing, detailing the action(s) taken or to be taken to bring the violative process or product into compliance within a specified time frame. Voluntary correction does not preclude the initiation of administrative and/or judicial action.

In determining whether quality systems deviations are sufficient to support legal action, consideration should be given to the significance of the device, the establishment's quality history, and whether the problem(s) is/are widespread or continuing.

a. Warning Letters

Issuance of all Warning Letters should follow Chapter 4 of the Regulatory Procedures Manual (RPM) http://www.fda.gov/ora/compliance_ref/rpm/. Consult the Office of Enforcement's (OE) Warning Letter page on ORA's intranet website for current instructions for obtaining Office of Chief Counsel (OCC) clearance and current approved Warning Letter templates.

Districts have DIRECT REFERENCE AUTHORITY for Warning Letters in certain areas which are described in Chapter 4 of the RPM.

NOTE: Regarding direct reference authority for Correction and Removal violations, Warning Letters should only be issued once the districts have checked with their District Recall Coordinator to confirm that the recall is Class I or II.

Districts should obtain CDRH concurrence before issuing Warning Letters related to refurbishing/reconditioning of used devices, reprocessing of single use devices, violations of Part 11 relating to of Electronic Records and Electronic Signatures and other areas as prescribed in Chapter 4 of the RPM.

If the district determines that issuance of the Warning Letter has resulted in appropriate corrections and corrective action by the establishment, the district should, within five (5) working days after confirmation of documented evidence, update the establishment's profile data in FACTS.

b. Violative Follow-Up Inspections

As stated in Part III of this Compliance Program, the post-inspection activities serve to advise manufacturers that the conditions identified by the investigator may be symptomatic of system problems, and that the manufacturer is responsible for investigating, identifying, and correcting system problems. The Warning Letter templates further direct the establishment to discuss in its response how it will address the system problems related to the conditions identified by the investigator.

After issuance of a Warning Letter for Quality System violations, the next inspection should be a Level 3 inspection, as explained in Part III of this program. Coverage is dependent upon whether the previous inspection was Level 1 or Level 2 as explained in that Part. When investigators identify the same or additional conditions that meet the criteria for Situation I, the district should consider subsequent enforcement actions, such as seizure, injunction, prosecution, or civil penalties. During Level 3 inspections, the investigator should work closely with the district compliance officer and, where appropriate, CDRH to assure that appropriate coverage is provided and deviations properly documented.

c. The Recidivist Policy -- Enforcement Strategy For Establishments With Repeated Violative Inspections

- (1) Some establishments have a high rate of recidivism. They have developed a pattern of correcting violative conditions in response to a Warning Letter or other administrative/regulatory action, and usually maintain those corrections long enough to pass the follow-up inspection. When FDA next inspects the establishment (sometimes, as a follow-up to a recall), the investigator identifies similar conditions that again meet the criteria for Situation I. This tendency toward recidivism is often due to the failure of the establishment to have an effectively established quality management system being implemented.
- (2) When dealing with another violative inspection for such an establishment, the district should consider using the following strategy:
 - (a) Issue a Warning Letter that follows the Recidivist Warning Letter approved template found on OE's Warning Letter page on the ORA intranet website. This Recidivist Warning Letter requests the manufacturer to submit to the district (for up to 2 years if the district believes that it is necessary) an annual certification by an outside expert consultant stating that it has conducted a complete audit of the establishment's quality management system relative to the requirements of the Quality System regulation. The

manufacturer should submit a copy of the consultant's report¹ and certification by the establishment's CEO stating that he or she personally has received and reviewed the consultant's report and that the establishment has made or taken all corrections and corrective actions identified in the report. To keep the process on track, schedules, milestones, update reports and other similar activities should be established between the firm and FDA, or by the firm after issuance of the Recidivist Warning Letter.

- (b) Compliance Officers have the option of limiting the review of the certification only to the extent necessary to confirm that the consultant and the establishment have met the requirements set forth in the Recidivist Warning Letter. Compliance Officers may also request a technical evaluation of the consultant's report by the appropriate branch within the Office of Compliance (OC) or Office of In Vitro Diagnostics (OIVD) at CDRH. Compliance Officers have no obligations, however, to send to the establishment comments regarding the adequacy of the consultant's report or the establishment's corrections.
 - (c) Follow-up inspections will normally be conducted 3 – 6 months after the establishment certifies that it has completed all corrections and corrective actions.
 - (d) If the follow-up inspection indicates that the corrections and corrective actions are satisfactory, the district should notify the establishment that it has no objections. The district office should update the profile data. The district should also remind the establishment that it should continue to submit to the district, in accordance with the schedule specified in the Recidivist Warning Letter, certification by an outside expert consultant. This certification should state that: it has conducted an updated audit; has certification by the establishment's CEO that any corrections and corrective actions noted to be necessary by the consultant have been made; and remains in compliance with the requirements of the Quality System regulation. The establishment should continue to submit copies of the audit results.
- (3) If conditions identified by the immediate follow-up inspection or subsequent inspections meet the criteria for Situation I, the district should consider action such as injunction or seizure per A.1 above and the RPM.

¹ Establishments may be asked to release consultant's reports as part of their voluntary agreement with FDA. Because of its voluntary nature, the request is not in conflict with 21 CFR 820.180(c).

- (4) If the evidence indicates that the consultant's or establishment's certifications are fraudulent, the district is encouraged to advise and seek assistance from the Office of Criminal Investigations. When there is clear evidence that the establishment falsified its status report to the district, the district should initiate appropriate action under 18 USC 1001.

d. Recalls

If the district believes that prompt removal of a violative device from channels of commerce is necessary, it should proceed in accordance with the requirements of 21 CFR § 806 and established recall procedures found in Chapter 7 of the RPM and 21 CFR Part 7 (Enforcement Policy), Subpart C (Recalls). In the event of serious adverse health consequences or a death, CDRH may order a firm to discontinue further distribution and advise customers of the problem, and may subsequently order the recall of a device to the user level in accordance with Section 518(e) of the Act.

e. Seizure

A seizure is an action that is intended to take quick control over the violative product and put it under the possession or custody of the Court. A seizure should be recommended, if appropriate, as stated in Chapter 6 of the RPM.

f. Administrative Detention/Seizure

Prior to invoking an administrative detention, for a period of 20 or 30 days, the district director should have reason to believe: (1) the device is misbranded or adulterated; (2) the establishment holding the device is likely to quickly distribute or otherwise dispose of the device; and (3) detention is necessary to prevent use of the device by the public until appropriate regulatory action may be taken by the Agency.

District Directors should consult via telephone with CDRH, OC, Office of the Director and the Office of Chief Counsel (OCC) concerning administrative detention. Concurrence should be given by the Director, OC, CDRH, based on a recommendation by the OC and/or OIVD staff and OCC staff.

The district should **immediately** recommend seizure of the detained devices to assure continued control of the violative device after the 20/30 days of administrative detention expire.

g. Injunction

If an establishment has a continuing pattern of significant deviations in spite of past warnings, injunction will usually be the recommended action of choice. If a

serious health hazard exists, the recommendation should include a request for a temporary restraining order (TRO) to prevent the distribution of devices that have been manufactured under the violative conditions documented by the inspection report per the instructions in Chapter 6 of the RPM.

The recommendation should be accompanied by copies of all necessary documents, e.g., complete inspection reports, Warning Letters issued, sample analyses reports, establishment's response(s) to Warning Letters and/or Form FDA-483.

In the absence of physical samples, the inspectional evidence should clearly show that the establishment has deviated from the requirements of the Quality System regulation and/or other regulations, and the establishment meets the requirements of OAI. These deviations should be well documented and should show continuing system deficiencies, not just an isolated event.

h. Citation

A citation should be recommended, if appropriate, as stated in Chapter 5 of the RPM.

i. Prosecution

The criteria stated in Chapter 6 of the RPM are the criteria for consideration of prosecution of individuals in violation of the requirements of the Quality System regulation.

j. PMA Disapproval/Withdrawal

Refer to Compliance Program 7383.001, Part V.

k. Detention without Physical Examination

In general, detention without physical examination should be recommended by the Office of Compliance whenever there is documented evidence of an OAI situation for a foreign manufacturer when the criteria for a domestic seizure, injunction, or other regulatory remedies beyond a Warning Letter are met.

l. Civil Money Penalties

Section 303(f)(1)(B)(i) of the Act states that civil money penalties shall not apply to QS violations “unless such violation constitutes (I) a significant or knowing departure from such requirements, or (II) a risk to public health.” Section 303(f)(1)(B)(iii) further stipulates that civil penalties shall not apply to “section 501(a)(2)(A) which involve one or more devices which are not defective.”

For additional information, see the draft “Guidance for FDA Staff: Civil Money Penalty Policy” at the following link:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077927.htm>. Also refer to “Guidance for Industry and FDA Staff: Reduction of Civil Money Penalties for Small Entities” at
<http://www.fda.gov/OHRMS/DOCKETS/98fr/010049gd.pdf>.

5. Facilitating Review of Regulatory Recommendations

- a. The district should contact the appropriate CDRH/OC Division Director or the CDRH/OIVD Deputy Director by phone when the district believes they have an OAI situation for which a recommendation for seizure, injunction, civil penalties, or prosecution may be appropriate.

CDRH fully supports the concept of “Up Front” loading, so as to be fully aware of a potential situation and to provide guidance on how to proceed. At the discretion of the district, notification to CDRH may occur prior to an inspection, while the inspection is ongoing, or after issuance of the Form FDA-483. Notification would typically be made by a compliance officer, but could be made by the investigator and/or district management. The CDRH/OC and CDRH/OIVD organization charts are shown in Attachment A and B, respectively.

- b. When the district knows a regulatory action will be recommended as a result of the inspection, it should provide a copy of the issued Form FDA-483 to the appropriate division in OC or OIVD via email, as well as uploading the FDA-483 into CMS. The review process can begin within CDRH while the EIR and recommendation are being written by the district. A copy of the Form FDA-483 annotated with exhibit numbers, and EIR page numbers, helps the reviewers.
- c. It is the responsibility of district management to ensure that the documentation and evidence presented with each legal action recommendation is sufficient to justify and support each charge. The material submitted should include only the basic documentation needed to support each QS charge/example.
- d. All necessary samples and other supporting documentation should be tabbed and their location cross referenced in the recommendation in order to facilitate a timely review. It is highly recommended that you provide a table that cross references the violation with the Form FDA-483 item number, the inspection report page number and the exhibit number.
- e. All significant questions, problems, or other weaknesses in the evidence regarding the recommended action should be stated, along with pertinent district comments. Deficiencies/observations should be presented in descending order of importance.

- f. The recommendation should begin with the most serious deviation from the regulations with reference to the EIR pages, exhibits and sample results that document the violation. Each charge should be parenthetically referenced in the recommendation memorandum and the page location of the supporting evidence given. Each deviation should be related to its effect on device quality in light of overall controls, and should be separated according to the type of manufacturing activity.
- g. Physical samples are not required to support QS deviations, and should not be routinely collected for QS cases. If the district should reference violative documentary or physical samples as evidence to support QS deviations, the results should be tied to the QS deviation to show a cause/effect relationship.
- h. Information regarding previous warning and other past or ongoing regulatory actions should be referenced along with a description of corrections and corrective actions. If the recommendation or current EIR references a previous report, the district should copy the cited EIR pages.
- i. All legal action recommendations should be uploaded and processed in CMS.

B. MDR REGULATORY/ADMINISTRATIVE FOLLOW-UP
(SEE ATTACHMENT C)

The district should consider a Warning Letter when the following MDR violation(s) was/were disclosed during the inspection. This list only provides examples and is not all-inclusive.

- Firm fails to report, within five workdays, after becoming aware that a reportable MDR event necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health.
- Firm fails to submit an MDR death report.
- Firm fails to submit an MDR serious injury report.
- Firm fails to develop, maintain and implement written MDR procedures.

When the firm has already received a Warning Letter for MDR violations and still fails to comply with the MDR regulation, then the district should consider recommending a seizure, injunction, civil money penalty or prosecution.

All failures to comply with MDR should be listed on the FDA-483.

IMPORTANT NOTE: Warning Letters based on failure to report malfunctions should have CDRH review/concurrence per the instructions in Chapter 4 of the RPM.

C. TRACKING REGULATORY/ADMINISTRATIVE FOLLOW-UP
(SEE ATTACHMENT D)

The district should consider a Warning Letter when the following tracking violation(s) was disclosed during the inspection. This list only provides examples and is not all-inclusive.

- Firm distributes tracked device and does not have a tracking system.
- Firm does not have written standard operating procedures for collection, maintenance and auditing of the data for its tracked device(s).
- Firm's tracking system is ineffective in locating tracked devices during recall/notification.
- Firm does not perform audits of their tracking system.

When the firm has already received a Warning Letter for tracking violations and still fails to comply with the tracking regulation, then the district should consider recommending a seizure, injunction, civil money penalty or prosecution.

All failures to comply with the tracking regulation should be listed on the FDA-483.

IMPORTANT NOTE: CDRH concurrence is required for a Warning Letter for any violation of device tracking regulation requirements other than failure of the firm to implement any form of tracking system per the instructions in Chapter 4 of the RPM.

D. CORRECTIONS AND REMOVALS REGULATORY/ADMINISTRATIVE FOLLOW-UP
(SEE ATTACHMENT E)

The district should consider a Warning Letter when the following Corrections and Removals regulation violation(s) was/were disclosed during the inspection. This is only an example and is not all-inclusive.

- Firm fails to submit a Corrections and Removals report to the District within 10 working days of initiating a corrective action which would involve a Class I or II recall situation.

When the firm has already received a Warning Letter for Corrections and Removals violations and still fails to comply with the Corrections and Removals regulation, then the district should consider recommending a civil money penalty or prosecution.

All failures to comply with the Corrections and Removals regulation should be listed on the FDA-483, once the investigator has confirmed with their District Recall Coordinator that the situation would likely be classified as a Class I or II recall situation.

E. REGISTRATION AND LISTING REGULATORY/ADMINISTRATIVE FOLLOW-UP

Chapter 4 of the RPM states agency policy is that Warning Letters should only issue for violations of regulatory significance. Generally, registration and listing violations, as a sole finding, should not be the basis of a Warning Letter.

However, when those violations are found in combination with other findings, such as quality system violations, they should be included on the Warning Letter, after CDRH concurrence.

F. RADIATION EMITTING DEVICE REGULATORY/ADMINISTRATIVE FOLLOW-UP

Refer to Part V in Compliance Programs 7385.014, 7386.001, 7386.002; and 7386.004 through 7386.007 for guidance on regulatory actions related to radiation emitting devices.

G. EXPORTS REGULATORY/ADMINISTRATIVE FOLLOW-UP

When violations meet the criteria for Situation I for those unapproved devices exported under Section 802, note that fact in the Warning Letter. Submit a copy of the Warning Letter to CDRH, Division of Risk Management Operations, Regulatory Policy and Systems Branch with a recommendation to rescind all current or unexpired certificates of export.

PART VI

REFERENCES AND PROGRAM CONTACTS

A. APPLICABLE REFERENCES

1. Guide to Inspections of Quality Systems, August 1999
(<http://www.fda.gov/downloads/ICECI/Inspections/UCM142981.pdf>)
2. Code of Federal Regulations, Title 21, Part 7, Subpart C, Recalls.
Code of Federal Regulations, Title 21, Part 11, Electronic Records and Electronic Signatures.
Code of Federal Regulations, Title 21, Parts 16 and 17, Hearing Procedures.
Code of Federal Regulations, Title 21, Part 800, Subpart C, Administrative Detention.
Code of Federal Regulations, Title 21, Part 803, Medical Device Reporting.
Code of Federal Regulations, Title 21, Part 806, Reports of Corrections and Removals.
Code of Federal Regulations, Title 21, Part 807, Establishment Registration and Device Listing.
Code of Federal Regulations, Title 21, Part 809.10, Labeling For In Vitro Diagnostic Devices.
Code of Federal Regulations, Title 21, Part 810, Medical Device Recall Authority.
Code of Federal Regulations, Title 21, Part 820, Current Good Manufacturing Practices/Quality System Regulation.
Code of Federal Regulations, Title 21, Part 821, Tracking Requirements.
Code of Federal Regulations, Title 21, Parts 1000–1050, Radiation Regulations and Standards.
3. Federal Food, Drug, and Cosmetic Act, As Amended
(<http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm>)
4. Investigations Operations Manual (IOM) - Chapter 5, Subchapter 5.6, Devices
(http://www.fda.gov/ora/inspect_ref/iom/)
5. Biotechnology Inspection Guide, Reference Materials and Training Aids, November 1991
(<http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074181.htm>)
6. Medical Device Quality Systems Manual: A Small Entity Compliance Guide, HHS Pub. No. FDA 97-4179, December 1996 (<http://www.fda.gov/cdrh/dsma/gmpman.html>)
7. Calibration and Related Measurement Services of the National Institute of Standards &

- Technology, NIST Special Publication 250, National Institute of Standards & Technology, U.S. Department of Commerce, Washington, D.C. 20234.
8. Quality Management Systems – Process Validation Guidance, GHTF/SG3/N99-10:2004 Edition 2
(http://www.ghtf.org/documents/sg3/sg3_fd_n99-10_edition2.pdf)
 9. Implementation of Risk Management Principles and Activities Within a Quality Management System, GHTF/SG3/N15R8/2005
(<http://www.ghtf.org/documents/sg3/sg3n15r82005.pdf>)
 10. Intercenter Agreement Between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health, October 31, 1991
(<http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121175.htm>)
 11. Glossary of Computerized System and Software Development Terminology, August 1995
(<http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074875.htm>)
 12. Juran's Quality Handbook, Joseph Dufeo and J.M. Juran, 6th edition, McGraw-Hill, 2010.
 13. AQL Inspector's Rule and Manual. This special purpose plastic slide rule that rigidly adheres to ANSI/ASQ Z1.4 can be obtained from INFO P.O. Box 58, Stillriver, MA. 01467. Phone (978) 456-3848. Cost is approximately \$25 plus shipping cost for rule and manual. Information regarding the AQL Inspector's Rule and Manual can be found at the following web site: <http://www.aqlinspectorsrule.com>
 14. Medical Device Reporting for Manufacturers, March 1997
(<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094529.htm>)
 15. Do It By Design: An Introduction to Human Factors in Medical Devices, December 1996
(<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm095061.pdf>)
 16. The FDA and Worldwide Quality System Requirements Guidebook for Medical Devices, 2nd Edition, Daniel Amiram and Edward Kimmelman, ASQ Quality Press, Milwaukee, Wisconsin, 2008.
 17. Design Control Guidance for Medical Device Manufacturers, March 1997

- (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070642.pdf>)
18. Compliance Guide for Laser Products, June 1992
(<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM095304.pdf>)
 19. Guide to Inspections of Electromagnetic Compatibility Aspects of Medical Device Quality Systems, December 1997
(<http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074885.htm>)
 20. Medical Glove Guidance Manual, January 22, 2008
(<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073359.pdf>)
 21. Guidance for Industry and for FDA Staff: Enforcement Priorities for Single-Use Devices Reprocessed by Third Parties and Hospitals, August 14, 2000
(<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107164.htm>)

Copies of CDRH QS publications and FDA guidance documents are available from the Division of Small Manufacturers International and Consumer Assistance (DSMICA), Telephone: 800-638-2041 or FAX 301-847-8149 or Email at: dsmica@fda.hhs.gov. Many of these publications are also available in the CDRH Good Guidance Practices (GGP) Database (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm>).

Sources to obtain copies free of charge:

Internet (World Wide Web): FDA, CDRH, and ORA maintain web sites for easy access to information. The FDA home page is <http://www.fda.gov>; the CDRH home page is <http://www.fda.gov/cdrh/>; and the ORA home page is <http://www.fda.gov/ora/>.

Good Guidance Practices (GGP) Database: This is a searchable database that contains all current CDRH guidance documents and provides links to the documents.
(<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfggp/search.cfm>)

APPLICABLE REFERENCES – SPECIFIC TO STERILIZATION

The following sources may be referenced for further guidance regarding sterilization processes

Food and Drug Administration:

Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices, December 1987
(<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM080966.pdf>)

Updated 510(k) Sterility Review Guidance K90-1; Guidance for Industry and FDA, August 30, 2002
(<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM072790.pdf>)

A searchable database of FDA-recognized standards is available at:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm>

A list of FDA-recognized standards related to sterilization of medical devices can be obtained by searching on the category “Sterility.”

United States Pharmacopeia (USP)/National Formulary (NF), current edition:

U. S. Pharmacopeial Convention, Inc.

12601 Twinbrook Parkway

Rockville, Maryland 20852

<http://www.usp.org>

<http://www.uspnf.com> (USP/NF Online)

- <61> Microbial Limit Tests
- <71> Sterility Tests
- <85> Bacterial Endotoxins Test (LAL)
- <151> Pyrogen Test (USP Rabbit Test)
- <161> Transfusion and Infusion Assemblies and Similar Medical Devices
- <1211> Sterilization and Sterility Assurance of Compendial Articles
- <1035> Biological Indicators for Sterilization
- <55> Biological Indicator - Resistance Performance Tests
 - Biological Indicator for Dry-heat Sterilization, Paper Carrier
 - Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier
 - Biological Indicator for Steam Sterilization, Paper Carrier
 - Biological Indicator for Steam Sterilization, Self-Contained

B. PROGRAM CONTACTS

1. ORA Contacts

- a. Questions regarding inspectional requirements and/or technical assistance:

Division of Domestic Field Investigations
Medical Device Group
Telephone: (301) 827-5638

- b. Questions about accessing or connecting to the CDRH Center Information Retrieval System (CIRS):

Employee Resource & Information Center (ERIC)
Telephone: (301) 827-ERIC (3742)
<http://inside.fda.gov:9003/EmployeeResources/AboutEmployeeResourceInformationCenter/AboutERIC/default.htm>

The current procedure for ORA is to request access to enhanced CIRS via ERIC. OITCDRH will: 1) create an Oracle account, 2) enter user's name to a table that is used by the single sign-on, and 3) install the Jinitiator. After these three things are completed, user can access enhanced CIRS through the enhanced CIRS link in the CenterNet.

- c. Questions regarding sampling of devices and laboratory capabilities:

Lawrence D Hoostelaere
Division of Field Science (DFS), HFC-141
Telephone: (301) 827-1032

- d. WEAC contacts for testing medical devices:

Joseph Matrisciano, Jr.
Engineering Branch Chief, HFR-NE480
Telephone: (781) 756-9705

Pamela Mackill
Analytical Branch Chief, HFR-NE460
Telephone: (781) 756-9704

Brian Baker
WEAC Center Director, HFR-NE400

Telephone: (781) 756-9701

- e. Questions regarding COMSTAT:

GWQAP@fda.hhs.gov

Contact GWQAP Team Leader in Office of Enforcement

3. CDRH Contacts

NOTE: Refer to the CDRH/OC and OIVD Organizational Charts Attachment A and B respectively, to identify the unit within OC or OIVD that is responsible for the type of device for which you have a question or need guidance.

- a. MDR Regulation Interpretation and Policy Questions:

MDR Policy Branch
Division of Postmarket Surveillance
Office of Surveillance and Biometrics (OSB)
Email: rsmb@fda.hhs.gov
Telephone: (301) 796-6670
Fax: (301) 847-8135 (call or send email alert if sending a fax)

Data retrieval of MDR reports:

Information and Analysis Branch
Division of Postmarket Surveillance, OSB
Email: MDR.Requests@cdrh.fda.gov

- b. Questions regarding sampling and/or testing of general medical devices:

Kevin Milne
Office of Science and Engineering Laboratories
Telephone: (301) 796-2516
Email: kevin.milne@fda.hhs.gov

- c. Express Mail Address for All Regulatory Action Recommendations:

Field Operations Branch
Office of Compliance
Center for Devices and Radiological Health
10903 New Hampshire Avenue

Silver Spring, Maryland 20993-0002

- d. Questions regarding the interpretation and applicability of the device Quality System regulation and GMP exemptions:

Kimberly A. Trautman
Quality Systems/GMP Expert
Telephone: (301) 796-5515
Email: kimberly.trautman@fda.hhs.gov

Jan Welch
Quality System/IVD Expert
Telephone: (301) 796-5776
Email: jan.welch@fda.hhs.gov

- e. Questions regarding the reprocessing of single-use devices:

Larry D. Spears
Office of Compliance
Telephone: (301) 796-5517
Email: larry.spears@fda.hhs.gov

- f. Questions regarding compliance of medical device software, quality system software, or production/manufacturing equipment software:

John F. Murray, Jr.
Software Compliance Expert
Telephone: (301) 796-5543
Email: john.murray@fda.hhs.gov

- g. Questions regarding sterilization:

Check CDRH web site for current list of experts:

<http://inside.fda.gov:9003/PolicyProcedures/SOPsbyProgram/PeerReview/ucm011680.htm>

- h. Questions regarding Electronic Records and Electronic Signatures should be directed to:

John F. Murray, Jr.
Software Compliance Expert
Telephone: (301) 796-5543
Email: john.murray@fda.hhs.gov

- i. Questions regarding potential or proposed regulatory actions should be directed to the CDRH/OC Field Liaison:

David Kalins
Office of Compliance
Telephone: (301) 796-6612
Email: david.kalins@fda.hhs.gov

- j. Questions regarding compliance issues concerning in vitro diagnostic devices:

James Woods
Deputy Director, Patient Safety and Product Quality
Office of In Vitro Diagnostic Devices
Telephone: (301) 796-6225
Email: james.woods@fda.hhs.gov

4. FDA Web Sites:

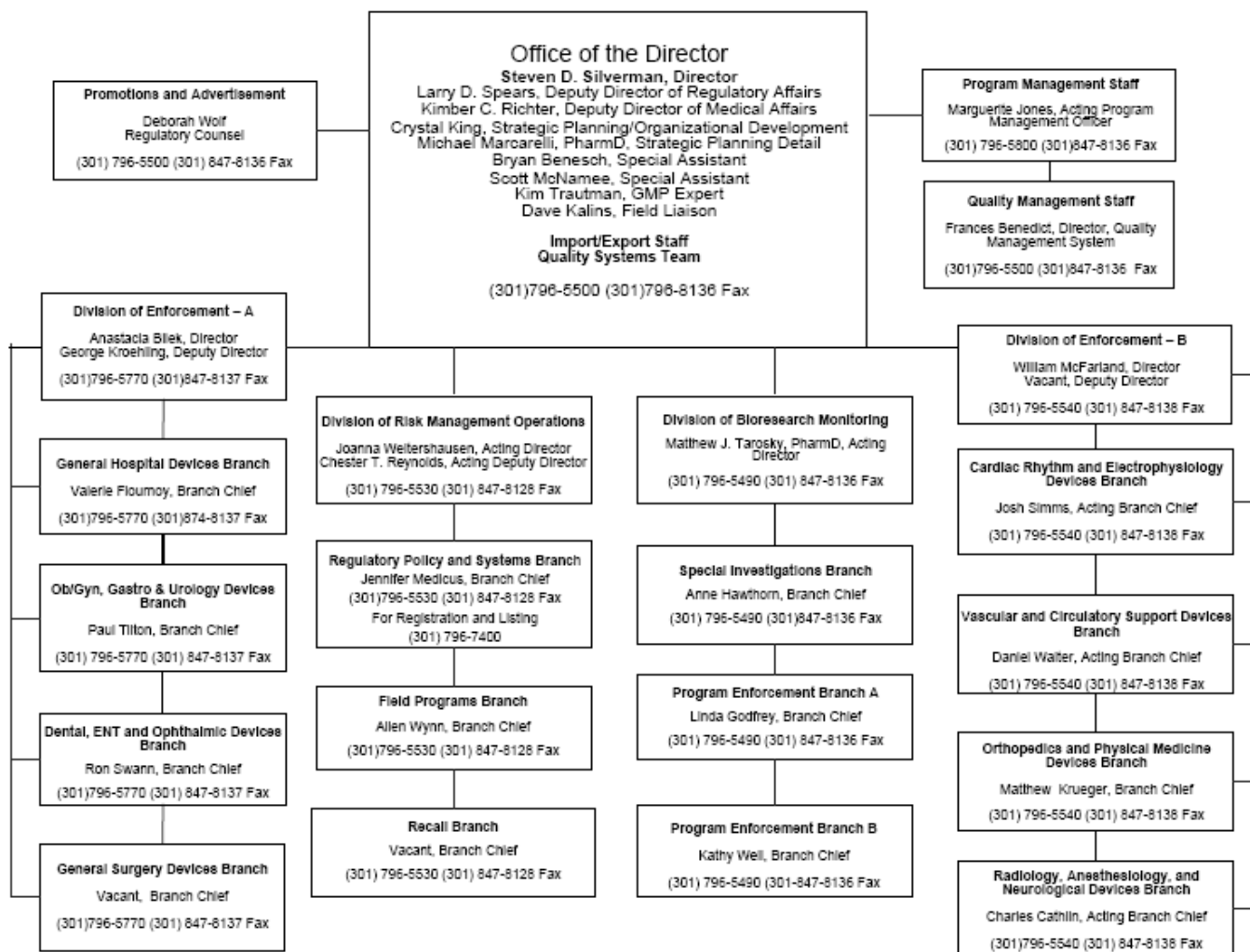
- a. FDA home page: <http://www.fda.gov>
- b. ORA home page: <http://www.fda.gov/ora/>
- c. CDRH home page: <http://www.fda.gov/cdrh/>
- d. MDR:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/default.htm>
- e. MedWatch: <http://www.fda.gov/medwatch>

<http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149238.htm>
(Instructions for completing MedWatch Form 3500A)
- f. QSIT Guide: <http://www.fda.gov/downloads/ICECI/Inspections/UCM142981.pdf>
- g. FDA Recognized Standards:
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm>

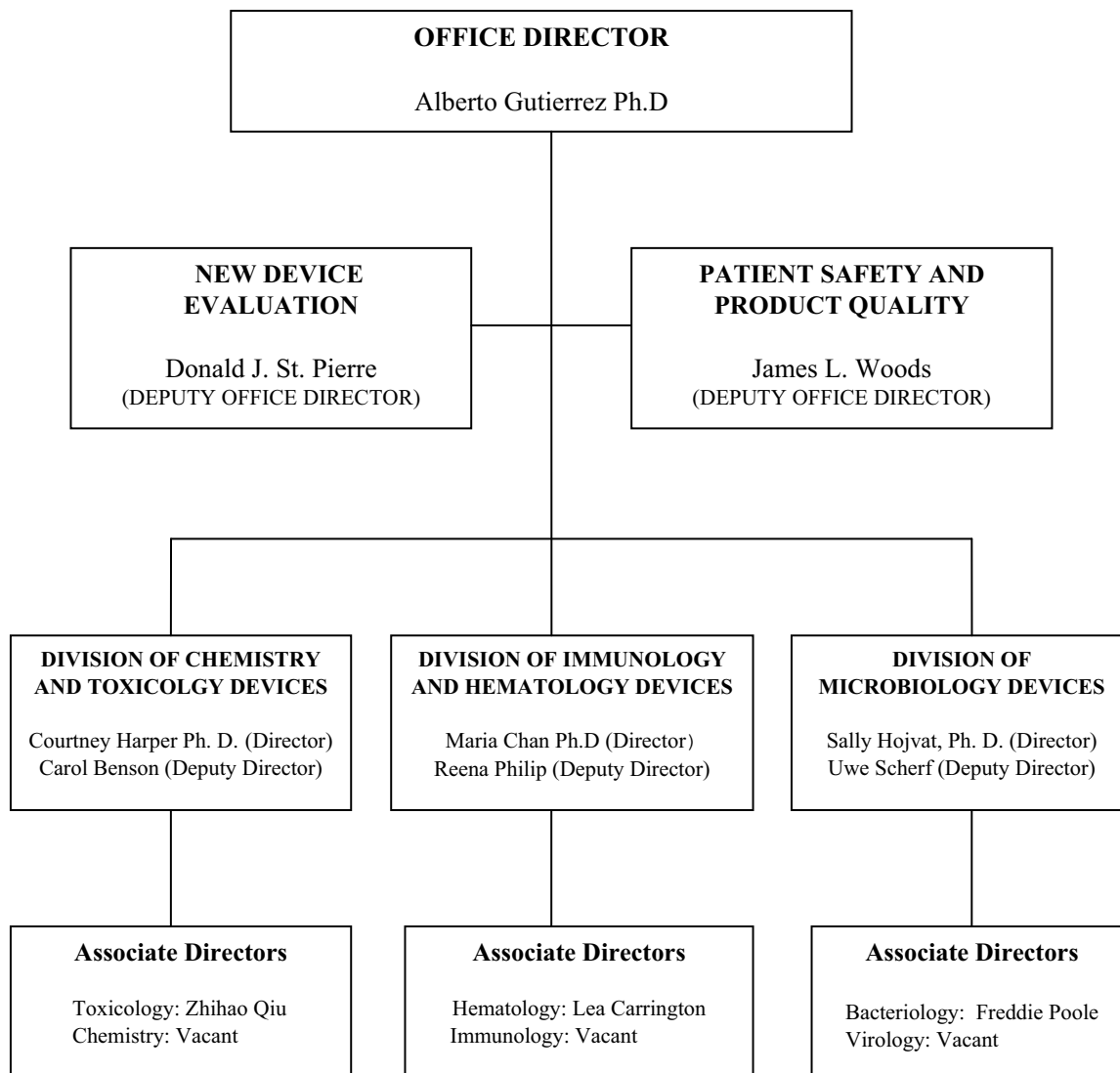
NOTE: A list of FDA-recognized standards related to sterilization of medical devices can be obtained by searching on the category “Sterility.”

- h. The Biologics and Devices Intercenter Agreement:
<http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121175.htm>
- i. Electronic Records and Electronic Signatures:
http://www.fda.gov/ora/compliance_ref/part11/
- j. Field Accomplishments and Compliance Tracking System (FACTS):
<http://web.ora.fda.gov/factsite/default.htm>
- k. Medical Device Tracking:
<http://www.fda.gov/cdrh/comp/guidance/169.html>
- l. Registration and Listing Database (files to be downloaded):
<http://drsm-sun2.cdrh.fda.gov:7784/cirs/cirs.do>
- m. Establishment Registration Database (searchable):
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/registration.cfm>
- n. Device Listing Database (searchable):
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/listing.cfm>
- o. Electronic Product Radiation Requirements:
<http://www.fda.gov/Radiation-EmittingProducts/ElectronicProductRadiationControlProgram/default.htm>
- p. Single-Use Device Reprocessing:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ReprocessingofSingle-UseDevices/default.htm>
- q. Guidance for Industry and for FDA Staff. Enforcement Priorities for Single-Use Devices Reprocessed by Third Parties and Hospitals:
<http://www.fda.gov/OHRMS/DOCKETS/98fr/000053gd.pdf>
- r. Product Code Classification Database (searchable):
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpd/pcdsimplesearch.cfm>
- s. Good Guidance Practices Database (searchable):
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfggp/search.cfm>

OFFICE OF COMPLIANCE



**Office of In Vitro Diagnostic Device
Evaluation and Safety (OIVD)
ORGANIZATION CHART**



ATTACHMENT C

SUMMARY OF MDR REPORTING REQUIREMENTS

Individual Adverse Event Reports - 803.50

General Requirements:

- Manufacturers must submit death, serious injury, and malfunction reports within 30 days after they become aware of a reportable event.
- The information can come from any source.
- Devices that "may have caused or contributed" to a death or serious injury or a malfunction that would be likely to cause or contribute to a death or serious injury must be reported.

Reasonably known:

- Firms must provide all information that is reasonably known to them. FDA considers the following to meet this standard, i.e., any information:
 - that can be obtained by contacting a user facility, distributor, and/or other initial reporter,
 - in the manufacturer's possession,
 - that can be obtained by analysis, testing, or other evaluation of the device.

Information required to be reported:

- The form FDA 3500A is the primary reporting form for death, serious injury and malfunction events. With the exception of drug or biologic related items, all the fields must be completed or have an entry (NA, NI, or UNK) indicating why the information could not be obtained.

Missing Information:

- Manufacturers are responsible for obtaining and providing FDA with any information that is missing from reports that are received from user facilities, distributors, and other initial reporters.
- If a firm cannot provide complete information, it must provide a statement explaining why such information was incomplete and the steps taken to obtain the information.
- Any required information not available at the time of the report or obtained at a later date, must be forwarded to FDA in a supplemental report within one month of receipt.

Investigation:

- Manufacturers are responsible for investigating and evaluating the cause of each event.
- These investigations must follow the requirements in 21 CFR 820.198 and provide the information required on form FDA 3500A, Block H.6, H.7, and H.9.

Five-Day Reports - 803.53:

- Manufacturers must submit a five-day report on form FDA 3500A within five days under the following two conditions:
 - a. They become aware that an MDR reportable event, from any source, requires remedial action to prevent an unreasonable risk of substantial harm to the public health.

OR

- b. They receive an FDA written request for the submission of five-day reports.

Baseline Reports - 803.55:

- Manufacturers are required to submit a baseline report on FDA 3417 form when the device model is first reported under 803.50.
- Baseline Reports must be updated annually (if information changes) on the firm's scheduled registration date, as required by Part 807.21.

IMPORTANT NOTE: The following MDR requirements have been stayed or revoked:

1. Certification, 21 CFR 803.57.
2. Baseline Reports, only sections 21 CFR 803.55(b) (9) and (10), which correlate to items 15 and 16 on the Baseline Report form, FDA 3417.

Supplemental Reports - 803.56:

- Manufacturers are required to submit, within one month after receipt, any required information regarding deaths, serious injuries, and malfunctions that was not available to them when the initial report was submitted.

GENERAL MDR GUIDANCE

This document provides general guidance regarding the reporting of adverse events required by the Medical Device Reporting (MDR) Regulation.

A. PER SE RULE

This requirement no longer exists. Therefore, the submission of an event by a health care professional does not require the manufacturer to report the event based solely on the statements of a health care professional. The event must meet the reporting criteria in MDR to qualify as a reportable event.

B. REPORTING TIME FRAMES

Firms now have up to 30 CALENDAR days after they become aware of a device related death, serious injury or malfunction before they are required to submit a report to FDA.

C. FIVE-DAY REPORTS

Five-day reports are required in two circumstances. First, they are required if a manufacturer becomes aware that a reportable event, from any source of information, necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health. Second, five-day reports are required when a manufacturer becomes aware of an MDR reportable event for which FDA has requested a five-day report.

D. NON-REPORTABLE EVENTS

Firms must submit MDR reports when the reported information reasonably suggests an association between one of its devices and a reportable death, serious injury or malfunction. Under some circumstances, an adverse event may appear to trigger the requirement of submission of an MDR, but because information reveals the device did not cause or contribute to the death or serious injury, no MDR is required. Thus, as described below, a manufacturer will have to investigate the event in order to know if it should be reported.

A firm is required to submit an MDR report when it becomes aware of information reasonably suggesting that an event meets the criteria for reporting a Death, Serious Injury, or Malfunction. For example, a hospital informs a manufacturer that its device has failed and, as a result, a patient died. At this point, the firm has become aware of information that reasonably suggests they are in receipt of a reportable MDR event.

Next, the firm must investigate the report to determine its cause. Both the QS Regulation and MDR require investigation of complaints. During its investigation a firm may become aware of information that changes the initial report's conclusions. For example, the firm may find that its device was not involved in the death and could not have caused or contributed to the death. In these instances the firm would document the information that changes the association between

its device and the death. No report would be required if the death or other facts turn out to be incorrect. But, if the firm becomes aware of the identity of the device/firm that was associated with the death, the firm is responsible for forwarding the information to the FDA.

However, if the firm's investigation does not change the alleged association between the device and the death, the event must be submitted as an MDR report. In addition, if the firm's investigation produces information that would cause a person who is qualified to make a medical judgment to reach a reasonable conclusion that the device did not cause or contribute to a reportable MDR event, no report is required. This means that if a firm decides NOT to report an apparent device-related death, serious injury or malfunction, this decision must be made by a person that the regulation recognizes as qualified to make a medical judgment, i.e., a physician, nurse, risk manager, or biomedical engineer. Using the example above, if the firm's investigation yields an autopsy finding that the patient died from cancer, not the device, the firm could decide NOT to report as long as the decision is consistent with the regulation:

1. There is documented information that changes the association between the death and the device,
2. The decision is made by a person who is qualified to make a medical judgment, and
3. The conclusion reached by the person in item two is reasonable.

PLEASE NOTE THE FOLLOWING:

- Firms ARE NOT required to have every MDR report reviewed by a person qualified to make a medical judgment and/or a person with a medical degree or training. Individuals who are not qualified to make a medical judgment can review MDR reports and make decisions on the basis of facts but they cannot make decisions NOT to report MDR events that require medical judgment.
- In lieu of in-house or on-site qualified medical personnel or individuals qualified to make a medical judgment, the firm may use consultants.
- When reviewing a non-reportable event, validate and document the credentials of the individual making these decisions as well as the decision not to report the event.

E. INVESTIGATION

Firms are required to investigate EVERY device related death, serious injury and malfunction in accordance with QS regulation, 820.198. Failure to comply with this provision is a violation of BOTH the QS regulation and MDR. Manufacturers are also required to VERIFY information on each form FDA 3500A as well as make a good faith effort to obtain information that is missing/not provided by the reporter. If the firm cannot obtain the missing information, the MDR complaint files shall contain an explanation of why the information could not be obtained as well as documentation of the firm's efforts to obtain the missing information.

F. REASONABLY KNOWN INFORMATION

FDA considers information that can be obtained by contacting the reporter to be in the possession of a firm, and considers information that can be obtained by analysis, testing, or other evaluation of a device to be information that a firm is expected to REASONABLY know, obtain and report.

G. REASONABLY KNOWN/GOOD FAITH EFFORT

A firm must demonstrate that it exercised "good faith" in any failed attempts to obtain required data that is missing, incorrect, or that FDA considers to be reasonably known. While the concept of good faith is generally considered to be equivalent to "due diligence", CDRH has not developed a standard. However, the firm's procedures for obtaining missing information should appear under the "Internal Systems" section of its written MDR procedures. In addition, the Center believes that the parameters of good faith effort must, at a minimum, comport with the level of risk/nature of the device associated with the event being investigated.

H. SERIOUS INJURY

The interpretation of what constitutes a serious injury can be subjective and complicate the enforcement of MDR. The "unanticipated temporary impairment" part of the former serious injury definition has been rescinded, thus alleviating a source of subjectivity. In addition, the requirements that intervention be "immediate" and the concept of "probability" have also been removed from the serious injury definition.

The current MDR regulation states that a serious injury is an "injury or illness." This literally means that there has to be an injury that is life-threatening, results in permanent impairment/damage, or necessitates medical/surgical intervention to preclude permanent impairment/damage in order for an event to be reportable as a serious injury. If there is no injury attributable to the device, then there is no serious injury report, however, the event may qualify as an MDR reportable malfunction depending upon the circumstances.

The Center may decide to clarify the definition of serious injury. These categories will be provided to the field and the industry through MDR guidance documents and/or letters, as necessary.

I. MALFUNCTIONS

Malfunction reporting decisions have been the subject of concern by both industry and the FDA. Basically, a malfunction is an event that is likely to cause or contribute to either a death or serious injury, but some circumstance prevented the injury or death from occurring. These events are very important since they represent "potential" deaths or serious injuries and provide the Agency with the opportunity to be proactive in reducing risks. Not all malfunctions, however, are MDR reportable events.

If a malfunction is not reportable as an MDR, it may be a complaint and thus subject to the QS complaint handling requirements. Determining if an event is a reportable malfunction involves answering a number of questions including:

1. Is the event device-related?
2. Has the device failed to perform its intended function or meet its performance specifications?
3. Is this failure likely to cause or contribute to a death or serious injury if the event were to happen again?

There is a presumption in the MDR regulations that if the event happened once it can happen again. The determination of whether to submit a report should be based on the potential outcome. For example, if this malfunction were to occur, how would it affect the patient? If the answer is "the malfunction is likely to cause or contribute to death or serious injury," then the event is reportable. The preamble to the MDR regulations (Federal Register: December 11, 1995, Volume 60, Number 237, pages 63577-63607) offers the following guidance for determining circumstances in which malfunctions should be reported:

1. The chance of a death or serious injury occurring as a result of the recurrence of the malfunction is not remote;
2. The consequences of the malfunction affect the device in a catastrophic manner that may lead to a death or serious injury;
3. The malfunction results in the failure of the device to perform its intended essential function and compromises the device's therapeutic, monitoring or diagnostic effectiveness, which could cause or contribute to a death or serious injury.

NOTE: The essential function of a device refers, not only to the device's labeled use, but for any use widely prescribed within the practice of medicine.

4. The malfunction involves a long-term implant or a device that is considered to be life-supporting or life-sustaining and, thus, is essential to maintaining human life. Malfunctions of long-term implants are not routinely or "automatically" reportable unless the malfunction is likely to cause or contribute to a death or serious injury if it recurs.
5. The manufacturer takes or would be required to take an action under sections 518 or 519(f) of the Act as a result of the malfunction of the device or other similar devices.

Conversely, malfunctions ARE NOT REPORTABLE if they are not likely to result in a death, serious injury, or another malfunction.

SOURCES OF INFORMATION:

WHERE TO OBTAIN MDR FORMS, GUIDANCE DOCUMENTS and OTHER MDR RELATED INFORMATION:

1. Division of Small Manufacturers, International and Consumer Assistance
Office of Communication, Education and Radiation Programs
Center for Devices and Radiological Health
10903 New Hampshire Avenue
WO66-4613
Silver Spring, MD 20993
Email: dsmica@fda.hhs.gov

Persons interested in obtaining a copy of the Final MDR Regulation published December 11, 1995 (document # 336) may either send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the document or send a fax request to 301-847-8149 to receive a hard copy. Please include the document number in the request.

A major revision of device problem codes was implemented July 1, 2009. Other codes are also being revised. The link to the revised and current codes is:

<http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/EventProblemCodes/ucm134751.htm>

2. Food and Drug Administration
MedWatch (HF-2)
5600 Fishers Lane, Room 17-65
Rockville, MD 20857
1-800-FDA-1088 (Press "0" to speak with a staff member) or 301-827-7240
NOTE: Voluntary FDA Form 3500 ONLY

<http://www.fda.gov/medwatch> and click on "Report a Serious Medical Product Problem Online".

4. MDR Policy Branch
Division of Postmarket Surveillance
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
10903 New Hampshire Avenue, WO66, room 3217
Silver Spring, MD 20993-0002
NOTE: Mandatory FDA FORMS 3500A and UF annual report FDA Form 3419 and instructions for each can be obtained from the web pages below

5. Web pages:

<http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>

The instructions for the Mandatory MedWatch Form, 3500A, are located at –

<http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149238.htm>

WHERE TO SUBMIT ALL MANDATORY MDR REPORTS

Food and Drug Administration
Center for Devices and Radiological Health
PO Box 3002
Rockville, MD 20847-3002

NOTE: Envelopes must be specifically identified with the type of report enclosed, e.g., Manufacturer Report, User Facility Report, Annual Report, Five-Day Report, Supplemental Report, etc.

ATTACHMENT D

SUMMARY OF TRACKING REQUIREMENTS

WHO IS SUBJECT TO TRACKING?

- Domestic/Foreign Manufacturers and Importers of tracked devices who have received a tracking order.

WHAT DEVICES ARE CURRENTLY SUBJECT TO TRACKING ?

- Refer to “Medical Device Tracking Guidance for Industry and FDA Staff” dated January 25, 2010, or access <http://www.fda.gov/cdrh/comp/guidance/169.html>.

MANUFACTURER'S TRACKING SYSTEM SHALL BE CAPABLE OF IDENTIFYING THE WHEREABOUTS OF TRACKED DEVICES IN THE FOLLOWING SCENARIOS:

A. TRACKED DEVICES THAT HAVE NOT YET BEEN DISTRIBUTED TO A PATIENT

- Upon request provide FDA, within 3 working days, the name, address and telephone number of the distributor, multiple distributor, or final distributor holding the device for distribution and the location of the device.

B. TRACKED DEVICES WHICH HAVE BEEN DISTRIBUTED TO/IMPLANTED IN A PATIENT

- Upon request provide FDA, within 10 working days:
 - the lot number, batch number, model number, or serial number of the tracked device or other identifier necessary to provide for effective tracking of the device.
 - the date the device was shipped by the manufacturer.
 - the name, mailing address, and telephone number of the prescribing/implanting physician.
 - the name, mailing address, and telephone number of the physician regularly following the patient if different than the prescribing/implanting physician.
 - if applicable, the date the device was explanted and the name, mailing address, and telephone number of the explanting physician; the date of the patient's death; or the date the device was returned to the manufacturer and permanently retired from use, or otherwise permanently disposed of.

C. TRACKED DEVICES WHICH ARE USED OUTSIDE DEVICE USER FACILITIES, INTENDED FOR USE BY MORE THAN ONE PATIENT, AND DISTRIBUTED TO THE MULTIPLE DISTRIBUTOR

- Upon request provide FDA, within 10 working days will provide:
 - the lot, model number, batch number, serial number of the device or other identifier necessary to provide for effective tracking of the device
 - the date the device was shipped by the manufacturer
 - the name, address and telephone number of the multiple distributor
 - the name, address, telephone number, and social security number (if available) of the patient currently using the device
 - the location of the device
 - the date the device was provided for patient use
 - the name, address, and telephone number of the prescribing physician
 - when applicable, the date the device was returned to the manufacturer, permanently retired from use, or otherwise permanently disposed of

D. FIRMS SHOULD MAINTAIN DOCUMENTATION OF PATIENT'S DECISION TO DECLINE TRACKING

STANDARD OPERATING PROCEDURES

- Manufacturers of tracked device shall establish a written SOP for the collection, maintenance and auditing of the data specified for tracking in 21 CFR 821.25.
- Written SOPs shall incorporate the following:
 - Data collection and recording procedures including explanations of when and why required data could not be collected
 - Recording all modifications or changes to tracking system or the data collected/maintained, including dates and reasons for the modification/changes
 - A quality assurance program that includes a statistically relevant audit at no less than 6 month intervals for the first three years of distribution and at least once a year

thereafter

- Manufacturers of tracked devices must keep current records in accordance with its SOPs for as long as the device is in use or distribution whether or not the tracked device is still being manufactured or being distributed.

NOTIFICATION

- When manufacturers of tracked devices become aware that a distributor, final distributor, or multiple distributor of the manufacturer's devices has failed to comply with their respective tracking obligations per 21 CFR 821.30, they are required to notify their local FDA District Office, as required by 21 CFR 821.25(d).
- When manufacturers of tracked devices permanently discontinue doing business, they are required to notify FDA at the same time they notify any government agency, court, or supplier, and provide FDA with a complete set of its tracking records and information, as required by 21 CFR 821.1(e).

EXEMPTIONS & VARIANCES, 21 CFR 821.2

- If the firm indicates they have an exemption or variance from tracking, verify/confirm that the document was issued by the OC, CDRH.

ATTACHMENT E

SUMMARY OF CORRECTIONS AND REMOVALS - 21 CFR 806 REQUIREMENTS

1. Reports of Corrections and Removals – 21 CFR 806.10

Each device manufacturer and importer shall submit a written report to FDA of any correction or removal of a device IF the correction or removal was initiated to:

- a) Reduce a risk to health posed by the device; or
- b) Remedy a violation of the act caused by the device which may present a risk to health.
- c) Reports in items (a) and (b) above are NOT required IF:
 - i. The information has already been reported to FDA under the MDR regulation, 21 CFR 803 or under 21 CFR 1004.

NOTE: The MDR report must:

- Be submitted within the 10 day reporting timeframe specified in 21 CFR 806.10, and
 - Contain all the information required in a Report of Correction and Removal as specified in 21 CFR 806.10(c)(1-13).
- ii. The correction or removal meets the following criteria:
 - When the action is taken to improve the performance or quality of a device but does not reduce a risk to health posed by the device or remedy a violation of the act caused by the device
 - Market withdrawals, 21 CFR 806.2(h) and 21 CFR 7.3(j) - a correction or removal of a distributed device that involves a minor violation of the act that would not be subject to legal action by FDA or that involves no violation of the act, e.g., normal stock rotation practices
 - Routine servicing, 21 CFR 806.2(k) - any regularly scheduled maintenance of a device, including the replacement of parts at the end of their normal life expectancy, e.g., calibration, replacement batteries, and responses to normal wear and tear. However, repairs of an unexpected nature, replacement of parts earlier than their normal life expectancy, or identical repairs or replacement of multiple units of a device, are not routine servicing. Such service should be “trended” to determine if a problem exists

- Stock recoveries, 21 CFR 806.2(l) and 21 CFR 7.3(k) - the correction or removal of a device that has not been marketed or that has not left the direct control of the manufacturer, i.e., the device is located on the premises owned, or under the control of, the manufacturer, and no portion of the lot, model, code, or other relevant unit involved in the corrective or removal action has been released for sale or use.
- d) The key concept for determining when an event is reportable is the definition of risk to health found in 21 CFR 806.2(j):
- i. A reasonable probability that use of, or exposure to, the product will cause serious adverse health consequences or death; (Class I Recalls) or
 - ii. That use of, or exposure to, the product may cause temporary or medically reversible adverse health consequences, or an outcome where the probability of serious adverse health consequences is remote, (Class II Recall).

NOTE: Assistance regarding risk to health determinations can be obtained from your district's recall coordinator or CDRH's recall staff in the Office of Compliance.

- e) Manufacturers and Importers are required to submit a Corrections and Removals report to the appropriate FDA District Office within 10 working days of the decision to initiate a correction. A list of the information required in the report is listed in 21 CFR 806.10(c)(1-13).
- f) A foreign manufacturer or owner or operator of devices must also submit reports of corrections and removals.

NOTE: The regulation does not specify where foreign device manufacturers should send their Corrections and Removals reports. FDA, however, expects foreign Corrections and Removals reports to be submitted to the District Office where the product is being imported.

2. Records of Corrections and Removals required to be maintained, but not required to be reported, to FDA - 21 CFR 806.20:

- a) Each device manufacturer and importer who initiates a correction or removal of a device that is NOT required to be reported to FDA under Section 806.10 shall keep a record of each correction or removal.
- b) Records of corrections and removals NOT reported to FDA must contain the following information:
 - i. The brand name, common or usual name, classification name, product code (if known), and the intended use of the device.

- ii. The model, catalog, or code number of the device and the manufacturing lot or serial number of the device or other identification number.
 - iii. A description of the event(s) giving rise to the information reported and the corrective or removal action that has been, and is expected to be taken.
 - iv. Justification for NOT reporting the correction or removal action to FDA, which shall contain conclusions and any follow-ups, and be reviewed and evaluated by a designated person.
 - v. A copy of all communications regarding the correction or removal.
- c) Manufacturers shall retain all records required under this section for a period of 2 years beyond the expected life of the device, even if the respective firm has ceased to manufacture or import the devices.

In addition, Corrections and Removal files/records must be transferred to any new/subsequent manufacturer or importer of the device and maintained for the required period of time.

REPORTS OF CORRECTIONS AND REMOVALS REFERENCE MATERIAL

- 1. Title 21 CFR Part 806, Medical Devices; Reports of Corrections and Removals.
- 2. Title 21 CFR Part 7, Enforcement Policy, (Recalls (Including Product Corrections)-Guidelines on Policy, Procedures, and Industry Responsibilities.
- 3. Title 21 CFR Part 803, Medical Device User Facility and Manufacturer Reporting.

국외 의약품 GMP 가이드라인 동향 모음집

발 행 일 2011년 11월 초판 발행

발 행 기 관 식품의약품안전평가원 의료제품연구부

발 행 처 제조품질연구팀

발 행 인 김승희

편집위원장 김동섭

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윤태호, 조수경, 성 실

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