행복한
대한민국을 여는
정부 3.0

의료기기 무균 입증 자료에 관한 가이드라인

2014. 11

식품의약품안전평가원
의 료 기 기 심 사 부

본 가이드라인은 멸균의료기기 품목허가 시 제출되는 무균상태입증 자료의 요건과 항목별 예시를 제공함으로써 민원업무의 편의성을 도모하고자 작성된 것으로써 일반적인 작성방향을 기술하고 있습니다.

본 가이드라인에 작성된 해설 및 예시는 규정의 이해를 돕기 위하여 작성된 것으로 법적 효력이 있는 사항이 아니며, 실제 민원 업무 신청 시에는 각 제품별 특성에 따라 다르게 작성되어야 합니다.

또한, 현재까지의 경험과 과학적 사실에 근거한 것이므로 새로운 과학적 근거가 있을 경우 또는 관련 규정의 개정에 따라 추후 변경될 수 있습니다.

제·개정 이력서

의료기기 무균 입증 자료에 관한 가이드라인

제·개정번호	승인일자	주요 내용
1	2014. 11. 25.	의료기기 무균 입증 자료에 관한 가이드라인 제정

머 리 말

의료기기 기술발달 및 의료서비스에 대한 수요 증가로 인해 인체이식 의료기기 등 멸균의료기기의 사용이 해마다 증가하고 있습니다. 의료기기 사용으로 인한 인체감염을 방지하고자 우리나라를 포함한 각국의 정부는 의료기기의 사전허가시 멸균여부를 반드시 확인하여 허가하고 있으며 안전성 확보를 위해 지속적으로 노력하고 있습니다.

이러한 노력의 일환으로 식품의약품안전평가원에서는 멸균의료기기에 대한 국제적 수준의 안전성을 확보하고 무균시험을 합리적으로 실시할 수 있도록 의료기기 무균시험 자료 제출방식을 개선한 바 있습니다. 멸균의료기기의 허가신청시 제품의 무균입증을 위해 제출하는 첨부자료의 인정범위를 개선하여 국제조화 되도록 하였으며, 무균시험을 제품의 특성에 따라 합리적으로 적용하도록 함으로써 업체의 부담이 대폭 감소될 수 있도록 개선하였습니다.

이에 우리 원에서는 제도개선에 따른 민원인의 이해를 돕고 멸균의료기기 허가신청시 첨부자료로 제출하는 무균 입증 자료의 요건 및 제출방법을 안내하고자 '의료기기 무균입증 자료에 관한 가이드라인'을 발간하게 되었습니다.

앞으로도 우리 원은 본 가이드라인을 지속적으로 수정·보완할 예정이며, 아울러 민원인들의 편의를 도모하기 위한 다양한 가이드라인 등을 추가 발굴하여 관련 업무 수행에 많은 도움을 드리고자 계속 노력하겠습니다.

감사합니다.

2014년 11월

식품의약품안전평가원장 

목 차

Ⅰ 목 적

본 가이드라인은 멸균의료기기의 허가신청시 첨부자료로 제출하는 무균 입증 자료의 요건 및 제출방법을 안내함으로써 민원인이 허가서류를 준비하는데 편의를 제공하고자 마련되었다.

Ⅱ 용어 정의

1. 멸균(sterilization)

물리적, 화학적 방법을 이용하여 포자를 포함하여 모든 종류의 미생물을 사멸시키는 과정

2. 무균(sterile)

생존 가능한 미생물이 없는 상태

3. 멸균의료기기(sterile medical device)

제조하는 과정에서 멸균공정을 거치는 의료기기로서 제품의 용기 또는 포장 등에 “멸균” 또는 “STERILE"의 문자, 멸균방법 또는 멸균연월일 등 멸균품임을 표시하는 제품

4. 밸리데이션(validation)

어떤 조작, 공정, 기계설비, 원재료, 동작 또는 시스템이 실제로 기대되는 결과를 얻는다는 것을 검증하고 문서화 하는 행위

5. 미생물(microorganism)

세균, 진균, 원충 및 바이러스 등 미세한 크기의 개체

6. 세척(cleaning)

표면으로부터 오염원이나 미생물을 제거하는데 사용하는 화학적 또는 물리적인 방법

7. 멸균도 보증수준(sterility assurance level, SAL)

멸균 후의 제품에 대해 한 개 미생물의 생존 가능성

8. 멸균공정(sterilization process)

규정된 멸균 요구사항을 달성하는 데 필요한 일련의 작업

9. 공정변수(process variable)

시간, 온도, 압력, 농도, 습도, 파장 등 멸균공정 조건

10. 공정 매개변수(process parameter)

공정변수에 대해 규정된 값

11. 공정 시험기기(process challenge device, PCD)

멸균공정에 대해 일정 수준 이상의 저항성을 갖도록 설계되고 공정성능을 평가하는 데 사용되는 시험물품

12. 과잉치사(overkill)

제품의 미생물과 동등이상의 저항성을 갖는 생물학적 표시기를 가지고 적어도 12 Spore Log Reduction(SLR)에 도달함을 증명하는 멸균 프로세스

13. 포자 감소인자(Spore Log Reduction, SLR)

특정 멸균조건에 노출된 생물학적 표시기의 포자(spore)의 객체 수 감소를 표현하기 위해 상용로그 형태로 표현되는 인자

14. 멸균제(sterilizing agent)

정의된 조건에서 멸균상태를 달성하기 위해 충분한 멸균작용을 하는 물리적 또는 화학적 물질

15. 바이오 버든(bioburden)

제품 또는 멸균포장에 생존 가능한 미생물 개체 수

16. 생물학적 표시기(biological indicator, BI)

특정한 멸균 처리에 대하여 명확한 저항을 제공하는 성장 가능한 미생물을 포함하는 시험장치

17. 성능 적격성평가(performance qualification, PQ)

실운전을 통하여 장치, 시스템 또는 제조공정이 정해진 작동 범위 내에서 정상적으로 작동됨을 나타내는 증거를 확보하고 문서화하는 과정

18. 제품군(product family)

재료 및 구조 등이 유사하고 동등한 수준의 멸균공정으로 처리될 수 있는 제품 집단

19. 전처리(preconditioning)

멸균의료기기 적재물 전체를 미리 정한 상태(온도, 습도 등)로 만들기 위한 멸균공정 내의 제품 처리 과정

20. 통기(aeration)

멸균공정의 일부로 멸균제 또는 그 반응물을 멸균의료기기로부터 미리 정한 수준까지 제거하는 공정

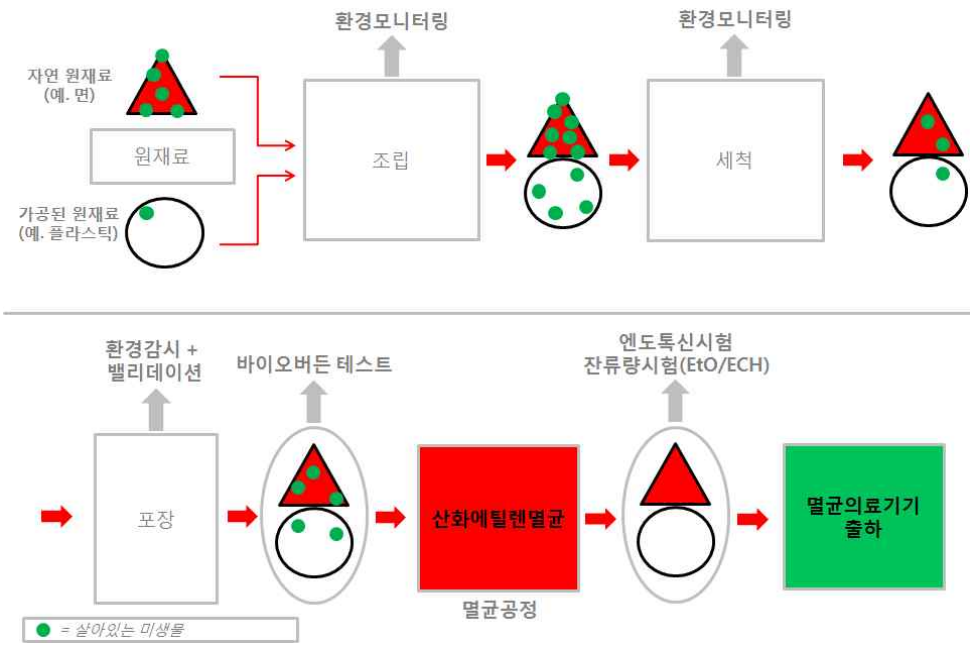
21. 반 공정(half cycle)

일상적으로 사용되는 멸균공정(full cycle)보다 50%정도 줄어든 시간으로 멸균하는 공정

Ⅲ 의료기기 멸균

1. 멸균의료기기의 제조공정

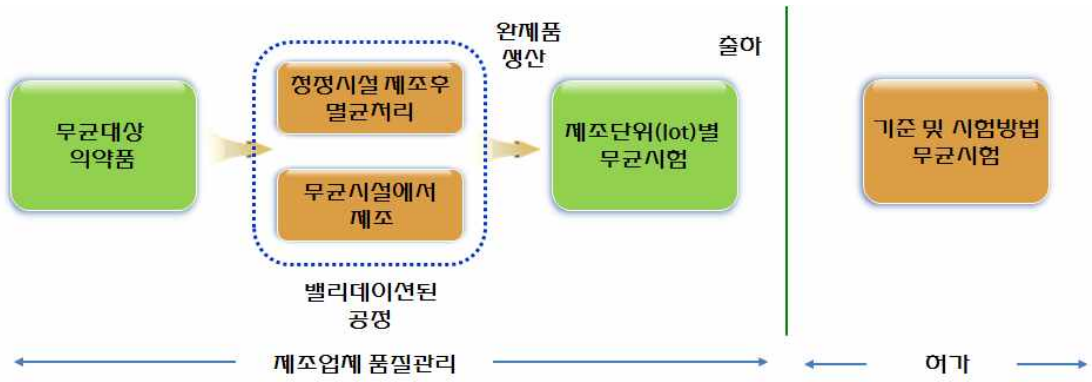
멸균의료기기는 미생물에 오염되었을 경우 환자에 감염을 유발할 수 있어 사용되기 전에 반드시 무균 상태이어야 한다. 일반적으로 멸균의료기기는 그림 1의 제조공정에서 보는 것과 같이 원재료 입고에서부터 제품 포장 전까지 세척(cleaning) 및 환경모니터링(environmental monitoring) 과정을 거쳐 미생물에 제품이 오염되지 않도록 관리하며, 최종적으로 멸균공정을 거치게 된다. 이러한 멸균공정은 '멸균도 보증수준'(sterility assurance level, SAL)에 따라 관리되는데, 멸균의료기기는 최소한 10^{-6}의 SAL을 가져야 한다.



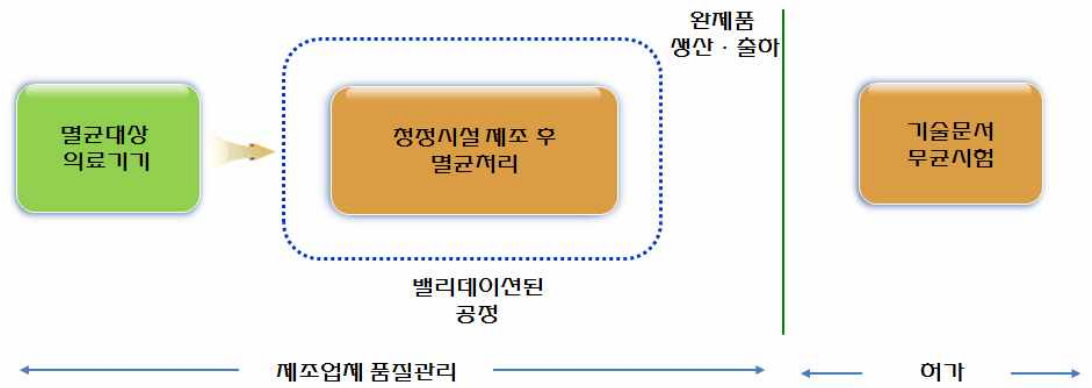
[그림1] 멸균의료기기의 일반적인 제조공정

2. 의료기기 멸균 밸리데이션

일반적으로 그림 2와 같이 무균시설에서 제조되는 의약품은 제조단위별(lot)로 대량생산되므로, 제조단위별 무균시험을 통해 제품의 무균을 보증하게 된다. 반면에, 일반적으로 다품종 소량생산 되는 멸균의료기기는 시료확보 등의 어려움이 있어 의약품과 같이 로트별 무균시험(Sterility Test)을 실시하기보다는 멸균 밸리데이션(validation)을 통해 제품의 무균을 확인한다.



<의약품 중 무균제품>



<멸균 의료기기>

[그림 2] 의약품과 의료기기의 일반적인 멸균방식

Ⅳ 의료기기의 무균 입증 방법

의료기기 업체가 허가 신청하고자 하는 멸균의료기기의 무균을 입증하기 위해서는 무균시험 성적서 제출 또는 무균 입증 자료를 제출이 가능하다.

1. 무균시험 성적서 제출을 통한 입증

의료기기 무균시험은 멸균된 제품에 감염원으로 적용될 수 있는 미생물(microorganism)이 존재하지 않음을 확인하는 시험으로 「의료기기 생물학적 안전에 관한 공통기준규격」에서는 대한약전과 이와 동등 이상의 시험방법에 따라 시험하도록 정하고 있다. 따라서 본 가이드라인에서는 대한약전의 무균시험을 통한 제품의 무균 입증 방법을 소개하고자 한다.

대한약전의 무균시험법에는 '무균확인 시험'과 '발육저지 활성확인 시험' 2개 시험항목을 제시하고 있다. '무균확인 시험'은 해당제품의 무균 상태임을 확인하는 시험이며 '발육저지 활성확인 시험'은 미생물의 대사활동, 단백질 합성, DNA 복제 등을 간섭하여 미생물의 성장을 억제하는 기전인 '발육저지 활성'이 있는지를 확인하는 시험이다.

두 시험항목 중 '발육저지 활성확인 시험'은 의료기기 적용 시 해당 제품의 특성을 고려하여 선택적으로 적용해야 한다. 예를 들면 의료기기에 약물이 포함되어 있거나 항균기능이 있는 제품에는 발육저지 확인시험이 필요하나, 그 이외의 제품에 적용은 바람직하지 않다. 따라서 품목허가 시 이러한 점을 유의하여 「의료기기 허가·신고·심사 등에 관한 규정」의 제29조 첨부자료의 요건에 적합한 시험성적서를 제출해야 한다.

2. 무균 입증 자료 제출을 통한 입증

허가 신청제품이 무균임을 입증하는 또 하나의 방법은 무균 입증 자료를 제출하는 방법이다. 기술문서 검토시 업체가 제출한 무균 입증 자료를 검토하여 제품이 무균임을 확인하는 것으로 국제조화된 방식이다.

의료기기 업체는 모든 제조단위의 멸균의료기기들의 무균을 보증하기 위해 멸균공정에 대하여 멸균 밸리데이션을 수행하게 된다. 이렇게 생산된 자료 중 품목허가 시 멸균의료기기가 '무균'처리 되었음을 입증하기 위해서는 아래의 자료가 검토되어야 한다. 또한, 동일한 멸균공정에서 이미 멸균도 보증수준(SAL)이 검증된 같은 제품군 내의 다른 제품과 부분품, 제조공정 등에 차이가 없거나, 차이가 있더라도 멸균성능에 영향을 미치지 않음을 입증할 경우에는 타 제품의 무균 입증 자료로도 무균 입증이 가능하다.

< 무균 입증 자료 >

가. 멸균제에 관한 자료

1) 멸균방법에 대한 설명 (방사선 멸균의 경우에는 조사량)

2) 멸균제 잔류량 최대 허용기준 및 설정근거

나. 멸균 밸리데이션 방법에 관한 자료

1) 멸균 밸리데이션 방법 설명 (밸리데이션 실측치 제외)

2) 밸리데이션에 참조된 관련규격 충족여부

다. 멸균도 보증수준(SAL)에 관한 자료

라. 엔도톡신 시험에 관한 자료 (혈액접촉·이식·중추신경계· non-pyrogenic 멸균의료기기에 해당)

1) 엔도톡신 시험 방법 설명

2) 시험기준 선정 및 해당 시험기준 충족여부

Ⅴ 무균 입증 자료의 요건 및 제출방법

1. 무균 입증 자료 요건 및 해설

가. 멸균제에 관한 자료

1) 멸균방법에 대한 설명 (방사선 멸균의 경우에는 조사량)

2) 멸균제 잔류량 최대 허용기준 및 설정근거

해 설

1) 멸균방법에 대한 설명

○ 멸균의료기기를 멸균하기 위해 사용되는 멸균제 종류(방사선, 산화에틸렌, 습열 등)에 대한 정보를 확인할 수 있는 자료를 제출한다.

- 참조할 수 있는 국제수준의 규격 등이 없는 멸균법이나 기타 필요한 경우, 멸균제 특성, 멸균 효과, 재질 특성변화 및 환경적 고려사항 등에 대한 자료가 추가적으로 요구될 수 있다.

○ 멸균공정에서 멸균의료기기의 안전성 및 유효성 등에 영향을 미칠 수 있는 공정매개변수에 대한 정보를 확인할 수 있는 자료를 제출한다.

- 멸균방법 별로 주요 공정매개변수는 다음과 같으며 대상 멸균의료기기 및 공정 특성 등에 따라 추가되거나 제외될 수 있다.

* 멸균방법 별 공정매개변수 예

· 방사선 멸균: 방사선원, 조사량, 조사시간 등

· 산화에틸렌(EO)멸균: 멸균제 노출시간, 농도, 온도, 습도, 압력 등

· 습열멸균: 멸균제 노출시간, 온도, 압력 등

2) 멸균제 잔류량 최대 허용기준 및 설정근거

○ 멸균제 잔류량 최대 허용기준 및 설정근거를 확인 할 수 있는 관련 규격과 해당 규격에서 제시하고 있는 기준 충족여부를 확인할 수 있도록 시험결과(실측치)를 포함한 자료를 제출한다.

- 산화에틸렌 잔류량 허용기준 등에 대해서는 「의료기기의 생물학적 안전에 관한 공통기준규격」 제7장(또는 ISO10993-7)을 참조할 수 있으며, 해당 자료는 관련 규격에 따른 잔류량 최대 허용기준과 시험결과에 따른 적합여부에 대한 정보를 포함하고 있어야 한다.

- 잔류량 최대 허용기준 등을 참조할 수 있는 국제수준의 규격 등이 없거나 기타 필요한 경우(예: 이산화염소가스멸균 등), 추가적인 근거자료가 요구될 수 있다.

나. 멸균 밸리데이션 방법에 관한 자료

1) 멸균 밸리데이션 방법 설명 (밸리데이션 실측치 제외)

2) 밸리데이션에 참조된 관련규격 충족여부

해 설

1) 멸균 밸리데이션 방법 설명

○ 멸균 밸리데이션 시험 절차 및 방법에 대한 근거(규격)와 해당 내용을 확인할 수 있는 자료를 제출한다.

- 일반적인 멸균 밸리데이션 절차는 다음과 같다. (ISO 11135-1 참조)

생물학적 표시기 및 생균수 법	과잉치사(overkill)법
· 제품 내 멸균하기 가장 어려운 위치에 생물학적 표시기(또는 기준 미생물)를 위치 함	· 제품 내 멸균하기 가장 어려운 위치에 생물학적 표시기(또는 기준 미생물)를 위치 함
· 생물학적 표시기(또는 기준 미생물)이 모두 불활성화 되지 않도록 멸균한 후 생물학적 표시기의 불활성화율을 계산함	· 일상적인 멸균 공정에서의 조건보다 낮은 노출조건으로 멸균을 실시하고, 제품내의 10^6 미생물을 불활성화하는 멸균 노출조건을 파악함
· 제품의 오염 미생물과 생물학적 표시기(또는 기준 미생물)의 불활성화율을 토대로 멸균요건을 달성하는데 필요한 멸균조건을 결정함	· 이것을 2회 이상 더 반복하여, 이 때 10^6 미생물의 불활성화가 확인된다면 멸균조건을 확대하여 멸균조건을 결정

- 멸균 밸리데이션 방법을 참조할 수 있는 국제수준의 규격 등이 없거나 기타 필요한 경우, 실측치 자료를 포함해 추가적인 근거 자료가 요구될 수 있다.

○ 멸균 밸리데이션 동안 사용된 대표제품과 생물학적 표시기(BI)를 멸균되기 가장 어려운 상황을 가정하여 선정하였음을 확인할 수 있는 자료를 제출한다.

- 대상 제품에 대해 일상적인 멸균공정에서 사용되는 적재 조합에서 요구되는 멸균도 보증수준(SAL)을 달성함을 확인하기 위해 제품군을 대표하는 제품이나 공정시험기기(PCD)를 사용하는 것이 일반적이다.
- 생물학적 표시기(BI)가 대상제품에서 예상되는 바이오버든의 수 보다 많고(SAL 10^{-6}를 입증할 수 있는 수준) 멸균제에 대한 저항성이 더 크다는 것을 입증할 수 있어야 한다.

○ 멸균 밸리데이션 동안 사용된 대표제품과 생물학적 표시기(BI)가 멸균되기 가장 어려운 장소에 위치되었음을 확인할 수 있는 자료를 제출한다.

- 제품 적재패턴의 변화는 멸균공정의 치사율을 감소시킬 수 있으므로, 허용 가능한 제품 적재패턴을 사전에 정의하는 것은 중요하다.
- 대상 멸균의료기기에 대해 정의된 멸균기 내 적재패턴에서 대표제품과 생물학적 표시기(BI)는 멸균되기 가장 어려운 장소에 위치해야 한다.

2) 밸리데이션에 참조된 관련규격 충족여부

○ ‘1) 멸균 밸리데이션 방법 설명’에 참조된 관련규격 리스트와 해당규격에 제시된 기준 충족여부를 확인할 수 있는 자료를 제출한다.

- 멸균방법 별로 적용 가능한 규격은 「의료기기 허가·신고·심사 등에 관한 규정」 [별표 2]를 참조할 수 있다.

다. 멸균도 보증수준(SAL)에 관한 자료

해 설

○ ‘나’항에 제시한 멸균 밸리데이션 방법에 따른 시험결과를 근거로 해당 멸균의료기기에 요구되는 멸균도 보증수준(SAL) 충족여부를 확인할 수 있는 자료를 제출한다.

○ 멸균 밸리데이션에서 사용된 생물학적 표시기(BI)의 무균여부를 확인 할 수 있는 자료를 제출한다.

- 과잉치사법에 따른 멸균 밸리데이션의 경우, 평가된 모든 공정(반 공정(half cycle)과 전체공정)을 거친 생물학적 표시기(BI)의 무균여부에 대한 정보를 포함하고 있어야 한다.

라. 엔도톡신 시험에 관한 자료 (혈액접촉·이식·중추신경계·non-pyrogenic 멸균의료기기에 해당)

1) 엔도톡신 시험 방법 설명

2) 시험기준 선정 및 해당 시험기준 충족여부

해 설

1) 엔도톡신 시험 방법 설명

○「대한민국약전」 [별표 5] 일반시험법 또는 이와 동등이상의 시험방법에 의해 시험을 수행하였음을 확인할 수 있는 자료를 제출한다.

2) 시험기준 선정 및 해당 시험기준 충족여부

○ 엔도톡신 시험기준 및 설정근거를 확인할 수 있는 관련 규격과 해당 기준 충족여부를 확인할 수 있는 자료를 제출한다.

- 동일 제조소 및 공정 내에서 제도된 다른 품목에 대한 자료 제출도 가능하다.
- 참조할 수 있는 국제수준의 규격 등이 없거나 기타 필요한 경우, 추가적인 근거자료가 요구될 수 있다.

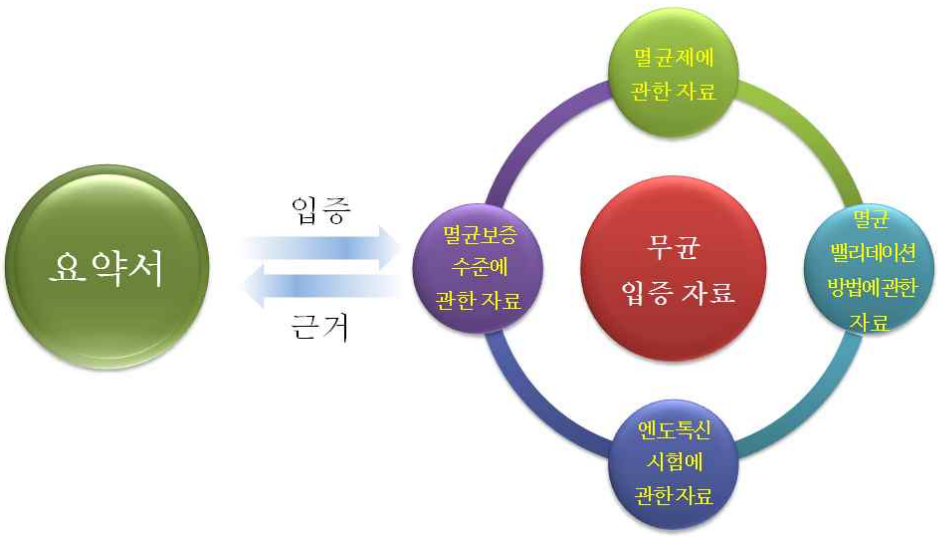
* 단, 국제수준의 규격 등을 근거로 엔도톡신 시험을 적용하지 않아도 됨을 입증하는 경우, 해당 자료의 제출이 면제 될 수 있다.

2. 무균 입증 자료의 제출방법

멸균 밸리데이션에 의해 생산된 자료는 각 제조사별, 품목별로 자료의 구성, 관리 및 작성방식 등이 다를 수 있고 그 내용 또한 방대하다. 따라서 품목허가 시 무균 입증 자료를 제출할 때에는 제품의 무균을 입증하는데 필요한 자료를 잘 정리해 제출하는 것이 중요하다.

「의료기기 허가·신고·심사 등에 관한 규정」의 제30조제3항에서는 외국의 자료는 주요사항을 발췌한 한글 요약문 및 원문을 첨부하도록 규정하고 있다. 따라서 외국의 자료는 허가심사에서 요구되는 자료 제출시 민원인에게 자료 준비에 대한 편의를 제공하고 심사 효율성을 제고하기 위해, 표 1과 같은 형식의 한글 요약문 및 무균 입증자료 원문 제출을 권고한다.

무균 입증 자료는 해당 자료에 대해 책임 있는 자의 서명 또는 직인, 발급기관에 대한 정보 등 자료의 신뢰성을 확인할 수 있는 내용을 포함하여 제출해야 한다.



[그림 3] 무균 입증 자료 제출

[표 1] 멸균의료기기 무균 입증 자료 요약문 양식 예

요건	내용 요약	첨부자료 (페이지)
가. 멸균제에 관한 자료	1) 멸균방법에 대한 설명 ① 멸균제 종류 ② 공정 매개변수 2) 멸균제 잔류량 최대 허용기준 및 설정근거* ① 잔류량 최대 허용기준 및 설정근거 ② 잔류량시험 적합여부	각 항목과 관련된 무균 입증 자료의 문서명 (해당 페이지)
나. 멸균 밸리데이션 방법에 관한 자료	1) 멸균 밸리데이션 방법 설명 ① 시험 절차 및 방법 ② 대표제품 및 BI 선정근거 ③ 대표제품 및 BI 제시방법 (적재패턴, 위치 등) 2) 밸리데이션에 참조된 관련규격 충족여부 ① 관련규격 또는 내부문서 리스트 ② 참조된 관련규격 또는 내부문서에 따른 기준 충족여부	
다. 멸균도 보증수준 (SAL)에 관한 자료	1) 요구되는 멸균도 보증수준(SAL)과 충족여부 ① SAL 충족여부 선언 ② 멸균공정을 거친 BI 무균여부	
라. 엔도톡신 시험에 관한 자료	1) 엔도톡신 시험 방법 설명 ① 시험 절차 및 방법 2) 시험기준 선정 및 해당 시험기준 충족여부 ① 시험기준 및 충족여부	

* 해당이 없을 경우 '해당 없음'으로 기재

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- Part1: Requirements for development, validation and routine control of a sterilization process for medical devices.

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[별첨 1] 무균 입증 자료 예시

앞서 가이드라인에서 설명한 무균 입증 자료에 대한 예시로 '산화에틸렌멸균'을 적용한 예이다.

요약문

요건	내용 요약	첨부자료 (페이지)
가. 멸균제에 관한 자료	1) 멸균방법에 대한 설명 ① 멸균제 종류: 산화에틸렌 (100% Ethylene Oxide(EO)) ② 공정 매개변수 (전처리) - 온도: ○ ~ ○℉ - 상대습도: ○ ~ ○% - 시간: ○ ~ ○분 (멸균제 노출) - 온도: ○ ~ ○℉ - 시간: ○ ~ ○분 - 압력: ○ ~ ○inHgA (통기) - 온도: ○ ~ ○℉ - 시간: ○ ~ ○분	① Certificate of Sterility(p.1) ② Certificate of Sterility(p.1), Report-9항.(p.7)
	2) 멸균제 잔류량 최대 허용기준 및 설정근거 ① 잔류량 최대 허용기준 및 설정근거: ISO 10993-7(2008) ② 잔류량시험 적합여부: 적합	① Report-1항.(p.2), 9항.(p.8) ② Report-9항. (p.8), Report-Index G(p.17)

요건	내용 요약	첨부자료 (페이지)
나. 멸균 밸리데이션 방법에 관한 자료	1) 멸균 밸리데이션 방법 설명 ① 시험 절차 및 방법 - ANSI/AAMI/ISO ISO 11135-1(2007)에 따름 - [과잉치사법] PCD/BI를 선정하여 멸균하기 가장 어려운 장소에 위치 → (생물학적 PQ) half cycle거친 BI가 무균임을 입증하여 Full cycle에서 SAL(12SLR)을 달성함을 확인 (4번의 half cycle과 1번의 full cycle) → (물리학적 PQ) 공정 매개변수의 재현성 확인 ② 대표제품 및 BI 선정근거 - 대표제품: 부분 공정에서 PCD와 대상제품을 멸균하여 PCD의 미생물이 더 많이 생존함을 보여줌으로써 PCD가 멸균되기 더 어려운 조건임을 입증 - BI: BI에 (SAL을 검증할 수 있는 미생물이 포함(3.5×10^6 CFU/BI)되어 있음을 확인했으며, 부분공정 결과를 비교하여 BI가 대상 멸균의료기기보다 멸균제에 대한 저항성이 높음을 확인 ③ 대표제품 및 BI 제시방법 - 적재패턴: 최대적재패턴과 최소적재패턴 정의 → 2번의 half cycle에서 각각의 적재패턴에 대해 상대습도분포 조사 → 최대적재패턴이 멸균되기 가장 어려운 적재패턴 결정됨 - 대표제품 및 BI 위치: half cycle와 full cycle에서 PCD 및 BI를 첨부자료의 그림과 같이 (균일하게) 위치시킴	① Report-Index A (p.12～p.16) ② Report-Index J (p.22～p.28) ③ Report-Index I (p.23～p.24), (p.26～p.27)

요건	내용 요약	첨부자료 (페이지)
나. 멸균 밸리데이션 방법에 관한 자료	2) 밸리데이션에 참조된 관련규격 충족여부 ① 관련규격 또는 내부문서 리스트 - ANSI/AAMI/ISO 11135-1 ISO 11135-1(2007): 과잉치사법을 통한 멸균 밸리데이션 - ISO 10993-7(2008): 멸균제 잔류량 최대 허용기준 및 적합여부 - Index A: 멸균 밸리데이션 세부 시험절차/방법 - Index I: 대표제품 및 BI 제시방법 - Index J: 대표제품 및 BI ② 참조된 관련규격/내부문서에 따른 기준 충족여부 - ISO 11135-1(2007)과 ISO 10993-7(2008)에 부합하며, 해당제품이 산화에틸렌 공정에서 멸균되는 것이 검증됨	 ① Report-2～4항. (p.2～p.3) ② Report-12항.(p.9)
다. 멸균도 보증수준 (SAL)에 관한 자료	1) 요구되는 멸균도 보증수준(SAL)과 충족여부 ① SAL 충족여부 선언 - 해당제품은 산화에틸렌으로 제시된 공정변수에서 멸균했을 때 SAL10^{-6}보증을 멸균 밸리데이션을 통해 입증함 ② 멸균공정을 거친 BI 무균여부 (과잉치사법) - (1차-half cycle)적합(16개의 BI에서 미생물증식이 없음) - (2차-half cycle)적합(16개의 BI에서 미생물증식이 없음) - (3차-half cycle)적합(16개의 BI에서 미생물증식이 없음) - (4차-half cycle)적합(16개의 BI에서 미생물증식이 없음) - (5차-fullf cycle)적합(8개의 BI에서 미생물증식이 없음)	 ① Certificate of Sterility(p.1) ② Report-9항. (p.5～p.7)

요건	내용 요약	첨부자료 (페이지)
라. 엔도톡신 시험에 관한 자료	1) 엔도톡신 시험 방법 설명 ① 시험 절차 및 방법 - 시험절차: USP LAL-gel-clot method - 시험방법: 해당제품을 상온에서 한 시간 동안 용출한 후 시험절차에 따라 시험함	① Endotoxin Analysis Certificate (p.35)
	2) 시험기준 선정 및 해당 시험기준 충족여부 ① 시험결과(<5EU/device)가 기준치(20EU/device)보다 낮으므로 적합함을 입증	① Endotoxin Analysis Certificate (p.35)

첨부자료

Certificate of Sterility

Product Name: ○ ○ ○
Manufacturer Facility: ○ ○ ○ 주소-○ ○ ○

Legal Manufacturer ○ ○ ○
REF # REF ○ ○ ○
Lot # ○ ○ ○, ○ ○ ○, ○ ○ ○, ○ ○ ○

가-1)-① 멸균제 종류

Sterility condition/Sterilization method	Sterile/Ethylene Oxide
Sterilization Site	○ ○ ○
Sterilization Cycle	○ ○ ○
Concentration of gas	100% EO
Temperature	○-○°F
Humidity	○-○%
Pressure difference at EO injection	○-○inHgA
Exposure time: Sterilization dwell:	○-○분
Aeration:	온도 = ○-○°F; 시간 = ○-○시간

가-1)-② 공정매개변수

[illegible]	Not applicable
Period of leave for de-gas for traditional cycles:	Not applicable
Packaging materials for device out to shelf carton	The ○ ○ ○ is packed in a hoop which is attached to a mounting card and then sealed in a Tyvek pouch. The pouch is then placed in a shelf carton with an IFU.

다-1)-① SAL 충족여부 선언

The sterilization cycle, Sterigenics Cycle 320, is validated to provide a sterility assurance level of 10^{-6} for the product listed above and the process is revalidated in accordance with ○ ○ ○

Final Disposition: APPROVED

Signature: ○ ○ ○
○ ○ ○
○ ○ ○

Date: ○.○.○

1/35

	Document number ○○○	Rev A	○○○
DESIGN HISTORY DOCUMENT	Title **REPORT, EO STERILIZATION VALIDATION,** CYCLE ○, CHANBER ○		

REVISION HISTORY

Rev	DCN	Change Description	Release Date
A		Initial release.	

1. OBJECTIVE

To validate the ethylene oxide sterilization process cycle○ for ○○○ Single Lumen Catheters, Balloon Catheters and Wire Devices using 100% ethylene oxide in chamber○ at ○○ ○○○

나-2)-① 관련규격/내부문서 리스트 and 32 box maximum loading configurations.

2. 가-2)-① 잔류량 최대 허용기준 및 설정근거

ISO 10993-7 (2008): Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals.

ANSI/AAMI/ISO 11135-1 (2007): Sterilization of healthcare products – Ethylene oxide – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices.

3. REFERENCE DOCUMENTS

Document No.	Rev	Document Description
○○○	A	Report, EO Sterilization Process Revalidation & Maximum Load Upsizing, ○○○ Cycle○
○○○	A	Report, EO Sterilization Process Revalidation, ○○○ Cycle○
○○○	A	Report, EO Sterilization Process Revalidation & Maximum Load Upsizing (30 Box), ○○○ Cycle○
○○○	A	Cycle Specification Agreement, EO Sterilization, ○○○/Chamber ○/Cycle○
○○○	T	EO Sterilization Controls

4. ATTACHMENTS

Attachment 1: ○○○ EO Sterilization Process Validation Final Report #○○ with the following indexes:

Index A	Validation Summary Report
Index B	Pre-sterilization Testing – PCD Preparation/BI Population Verification
Index C	Half Cycle #1 – BI Sterility/Temperature and Relative Humidity (RH) Distribution, 32 box maximum loading.
Index D	Half Cycle #2 – BI Sterility/Temperature and Relative Humidity (RH) Distribution, 1 box minimum loading.
Index E	Half Cycle #3 – BI Sterility/Temperature and Relative Humidity (RH) Distribution, 32 box maximum loading.
Index F	Half Cycle #4 – BI Sterility/Temperature and Relative Humidity (RH) Distribution, 32 box maximum loading.
Index G	Full Cycle – BI Sterility/Temperature and Relative Humidity (RH) Distribution/32 box maximum loading/Sterilant Gas Residue Analysis.
Index H	Test Procedures
Index I	Protocol
Index J	Referenced Testing – Comparative Resistance and Bioburden Resistance Studies

Attachment 2: Sterilization dunnage product assembly instructions and record for 1 box min and 32 box max load/ Product weight/density calculation data sheet.

2/35

Attachment 2: Sterilization dunnage product assembly instructions and record for 1 box min and 32 box max load/ Product weight/density calculation data sheet.

Attachment 3: ○○○ - Customer Order Forms dated ○○ and ○○ (four half-cycle and one full-cycle). Purchase order # ○○○ .

Attachment 4: ○○○ - Sample Submission Forms dated ○○ and ○○○ .

5. TEST ARTICLES

Dunnage test articles for this validation were chosen based on product density. Highest density represents the worst case condition. Packaged products from each of the three families (○○○ ○○○) were weighed and their densities calculated, see Attachment 2. The ○○○ family was found to have the highest density. A total of 2,304 devices, consisting of X5, X6, L4, L5 & L6 ○○○ , were packed into thirty-two shipper boxes for use as maximum load configuration in this validation, see Attachment 2 for assembly instructions and build record. A total of 72 devices were packed into one shipper box for use as a minimum load configuration.

The following product test articles were used for Sterilant Gas Residue Analysis testing.

Product Family	*Description*	*REF*	*Lot Number*	*Quantity*
Single-Lumen Catheters	○○○	○○○	○○○	9
Balloon Catheters	○○○○○○○○○	○○○	○○○	9
Wire Products	○○○	○○○	○○○	9

The following Process Challenge Devices (PCD) with enclosed biological indicators (BI) were used in this study:

Cycle	○○○ *Part Number*	○○ *Part Number*	*Quantity*	*BI Lot Number*
Half Cycle	○○○	○○○	60	○○
Full Cycle			17	

6. PROTOCOL DEVIATIONS

The temperature spec limit for the Aeration phase is between ○-○°F While running half-cycle # 2 and #4, the temperature dropped to ○°F cle #2) and ○°F cycle #4) for about 4 minutes. Per ○○○ , temperature spike (up and down) is common because products (from different customers) are frequently added to or removed from the room. It is a common practice to add extra aeration time to make up for the time the room went below the lower spec limit. For these two cycles, about 10 minutes extra was added to the aeration time as a result. This out of spec condition does not impact the acceptance criteria because approximately 10 minutes was added to compensate for the 4 minutes the temperature fell below ○°F .

7. TEST LABORATORY

○○○○○○○○○
○○○○○○○○○
○○○○○○○○○

○○○○○○○○○
○○○○○○○○○
○○○○○○○○○

8. STUDY DATES

Four half-cycles were performed from ○○.○○.○○ through ○○.○○.○○
One full-cycle was performed on ○○.○○.○○
All laboratory reports were completed on ○○.○○.○○

	Document number	Rev	
	○○○	A	
DESIGN HISTORY DOCUMENT	Title **REPORT, EO STERILIZATION VALIDATION,** CYCLE ○, CHAMBER ○		

9. RESULTS SUMMARY

Attachment	*Description*	*Acceptance Criteria*	*Results*
1 *Index B*	Final Report, Process Challenge Device Preparation ○○○○	Population verifications of organism must be performed. BIs must be within expiration date and have a certificate from the manufacturer.	Pass. Population verification was performed on July 12, 2011. BI expiration date was ○○○○○. Manufacturer's certificate was received from ○○○○○○
1 *Index B*	Report, Biological Indicator Population Verification ○○○○ Manufacturer's Certification for ○○○○	BI populations must be greater than 1.0×10^6 CFU/strip. They should also not exceed ○ log or fall under ○ log of the labeled population.	Pass. Average population at 48h: ○○○○: 4.5×10^6 CFU/strip. ○○○○: 4.0×10^6 CFU/strip. Manufacturer's labeled population: 3.3×10^6 CFU/strip. Difference in log value: ○○○○: 0.13 ○○○○: 0.08
1 *Index C*	Final Report, Biological Indicator Sterility Test – Half Cycle #1 (7 Day Incubation)	Per ISO 11135-1, no growth of the indicator organism in a half or full cycle.	Pass – no growth for 16 BIs
1 *Index C*	Temperature/Humidity Distribution Study – Half Cycle #1	Cycle parameters must meet ○○○ requirements. Results: Pass.	

다-1)-② 멸균공정을 거친 BI 무균여부

HALF-CYCLE #1	Acceptance Criteria	Actual Results
Preconditioning	Temp: 100 – 120°F	○-○°F
	RH: ○-○%	○-○%
	t: ○mins-○mins	○mins
Exposure (Dwell time)	Tem ○-○°F	○-○°F
	t: ○mins-○mins	○mins
	Pressure: ○-○inHgA	○-○inHgA
Aeration	Temp: ○-○°F	○-○°F
	t: ○mins-○mins	○mins

	Document number	Rev	
	○○○	A	
DESIGN HISTORY DOCUMENT	Title **REPORT, EO STERILIZATION VALIDATION,** CYCLE ○, CHAMBER ○		

Attachment	*Description*	*Acceptance Criteria*	*Results*
1 *Index D*	Final Report, Biological Indicator Sterility Test – Half Cycle #2 (7 Day Incubation)	Per ISO 11135-1, no growth of the indicator organism in a half or full cycle.	Results: Pass – no growth for 16 BIs
1 *Index D*	Temperature/Humidity Distribution Study – Half Cycle #2	Cycle parameters must meet Cycle ○ requirements. Results: Pass with deviation.	
1 *Index E*	Final Report, Biological Indicator Sterility Test – Half Cycle #3 (7 Day Incubation)	Per ISO 11135-1, no growth of the indicator organism in a half or full cycle.	Results: Pass – no growth for 16 BIs
1 *Index E*	Temperature/Humidity Distribution Study – Half Cycle #3	Cycle parameters must meet ○○○ requirements. Results: Pass.	

HALF-CYCLE #2	Acceptance Criteria	Actual Results
Preconditioning	Temp: ○–○°F	○–○°F
	RH: ○–○%	○–○%
	t: ○mins–○mins	○mins
Exposure (Dwell time)	Temp: ○–○°F	○–○°F
	t: ○mins–○mins	○mins
	Pressure: ○–○inHgA	○–○inHgA
Aeration	Temp: ○–○°F	○–○°F below 100°F for about 4 minutes). See Deviation section.
	t: ○mins–○mins	○mins

HALF-CYCLE #3	Acceptance Criteria	Actual Results
Preconditioning	Temp: ○–○°F	○–○°F
	RH: ○–○%	○–○%
	t: ○mins–○mins	○mins
Exposure (Dwell time)	Temp: ○–○°F	○–○°F
	t: ○mins–○mins	○mins
	Pressure: ○–○inHgA	○–○inHgA
Aeration	Temp: ○–○°F	○–○°F
	t: ○mins–○mins	○mins

	Document number	Rev	
	○○○	A	
DESIGN HISTORY DOCUMENT	Title **REPORT, EO STERILIZATION VALIDATION,** CYCLE ○, CHAMBER ○		

Attachment	*Description*	*Acceptance Criteria*	*Results*
1 *Index F*	Final Report, Biological Indicator Sterility Test – Half Cycle #4 (7 Day Incubation)	Per ISO 11135-1, no growth of the indicator organism in a half or full cycle.	Results: Pass – no growth for 16 BIs
1 *Index F*	Temperature/Humidity Distribution Study – Half Cycle #4	Cycle parameters must meet ○○○ requirements. Results: Pass with deviation.	
1 *Index G*	Final Report, Biological Indicator Sterility Test – Full Cycle (7 Day Incubation)	Per ISO 11135-1, no growth of the indicator organism in a half or full cycle.	Results: Pass – no growth for 8 BIs
1 *Index G*	Temperature/Humidity Distribution Study – Full Cycle	가-2)-② 잔류량시험 적합여부	

HALF-CYCLE #4	Acceptance Criteria	Actual Results
Preconditioning	Temp: ○-○°F	○-○°F
	RH: ○-○%	○-○%
	t: ○mins-○mins	○mins
Exposure (Dwell time)	Temp: ○-○°F	○-○°F
	t: ○mins-○mins	○mins
	Pressure: ○-○inHgA	○-○inHgA
Aeration	Temp: ○-○°F	○-○°F (below ○°F for about 4 minutes). See Deviation section.
	t: ○mins-○mins	○mins

Full-Cycle	Acceptance Criteria	Actual Results
Preconditioning	Temp: ○-○°F	○-○°F
	RH: ○-○%	○-○%
	t: ○mins-○mins	○mins
Exposure (Dwell time)	Temp: ○-○°F	○-○°F
	t: ○mins-○mins	○mins
	Pressure: ○-○inHgA	○-○inHgA
Aeration	Temp: ○-○%	○-○%
	t: ○mins-○mins	○mins

	Document number	Rev	
	○○○	A	
DESIGN HISTORY DOCUMENT	Title **REPORT, EO STERILIZATION VALIDATION,** CYCLE ○, CHAMBER ○		

가-2)-① 잔류량 최대 허용기준 및 설정근거

가-2)-② 잔류량시험 적합여부

Attachment	*Description*	*Acceptance Criteria*	*Results*
1 *Index G*	Final Report, Sterilant Gas Residue Analysis (Full Cycle at Day 3, 5, & 7 after completion of aeration)	ISO 10993-7 limits must be met at Day 5 after completion of aeration since this is the earliest possible product release date due to 5-day BI testing: EO – average daily dose to patient shall not exceed 4 mg. ECH – average daily dose to patient shall not exceed 9 mg. **Note:** Test articles were also tested at "Day 3" which provides further assurance of conformance to the requirement.	Results: Pass (ISO 10993-7) **Family 1: Single Lumen Catheters** Day 3 / Day 5 / Day 7 EO (mg/device): 0.0 / 0.0 / 0.0 ECH (mg/device): 0.0 / 0.0 / 0.0 **Family 2: Balloon Catheters** Day 3 / Day 5 / Day 7 EO (mg/device): 0.0 / 0.0 / 0.0 ECH (mg/device): 0.0 / 0.0 / 0.0 **Family 3: Wire Devices** Day 3 / Day 5 / Day 7 EO (mg/device): 0.0 / 0.0 / 0.0 ECH (mg/device): <0.0 / <0.0 / <0.0

Note: Temperature and Relative Humidity distribution studies were performed by ○○○ as reference only.

10. ROUTINE PROCESS CONTROL PLAN

The process will be routinely controlled in accordance with the procedures listed below (or equivalent):

○○ : Ethylene Oxide Sterilization Controls

○○ Cycle Specification Agreement, EO Sterilization, ○/○ Chamber ○/Cycle ○

○○ : Inspect Pre-Sterile Load

○○ : Final Inspect Sterile Load

11. REVALIDATION

The EO revalidation is to be performed every 24 months. Based on the December completion of this study, the next revalidation study is due in ○○ .

In addition, the need for revalidation will be considered before implementation of changes controlled per ○○

나-2)-② 참조된 관련규격/내부문서에 따른 기준 충족여부

12. CONCLUSIONS

The study objectives were met.

Compliance with ISO 11135-1 (2007) and ISO 10993-7 (2008) has been demonstrated.

Cycle○ is validated for the following loading configuration: 1-box minimum and 32-box maximum.

	Document number	Rev	
	○○○○○○	A	
ATTACHMENT	Title		
	SEE SHEET 1		

Attachment ○

Pages Attached ○○
(not including this sheet)

10/35

Table of Contents Lab #○○○

Index	Index Title	Testing Performed	Number of Pages
A	Validation Summary Report	N/A	○○
B	Pre-sterilization Testing	Process Challenge Device (PCD) Preparation / Biological Indicator (BI) Population Verification	○○
C	Half Cycle 1	BI Sterility / Temperature and Relative Humidity (RH) Distribution	○○
D	Half Cycle 2	BI Sterility / Temperature and RH Distribution	○○
E	Half Cycle 3	BI Sterility / Temperature and RH Distribution	○○
F	Half Cycle 4	BI Sterility / Temperature and RH Distribution	○○
G	Full Cycle 1	BI Sterility / Temperature and RH Distribution / Sterilant Gas Residue Analysis	○○
H	Test Procedures	N/A	○○
I	Protocol	N/A	○○
J	Referenced Testing	Comparative Resistance Study / Bioburden Resistance Study	○○

11/35

Ethylene Oxide (EO) Sterilization Process Validation Final Report

Test Article: 2011 Validation of New Chamber at ○○○○○
Laboratory Number: ○○○○○
Study Received Date: ○○○○○
Test Procedure(s): Standard Test Protocol (STP) Number: ○○○○○
Protocol Detail Sheet (PDS) Number: ○○○○○

나-1)-① 멸균 밸리데이션 방법 설명

Summary: This report summarizes the EO sterilization processes performed for the cycle validation intended to sterilize product with the appropriate microbicidal activity. Equipment commissioning and characterization, product definition, installation qualification (IQ) and operational qualification (OQ) are activities not included in the scope of this validation report and are the responsibility of the sponsor and contract sterilizer. The sterilization process definition and the performance qualification are included in this report. The validation of the sterilization cycle for the product produced by the sponsor has been successfully completed.

Contract Sterilizer:	○○○○○
	○○○○○
Chamber Number:	○○○○○
Chamber Volume:	○○○○○
Loading Configuration:	Minimum load consisting of one shipper box on one pallet Maximum load consisting of thirty-two shipper boxes (Two total pallets, sixteen shipper boxes per pallet)
Configuration Product Volume:	≤○○ (based on the Maximum Load Volume)
Full Cycle Number:	○○
Half Cycle Number:	○○
Type of Product Used:	○○○○○
Product Name:	○○○○○○○○○○○○○○○○
Method in which Pallets were Secured:	○○○○○
Internal Process Challenge Device (PCD) Type:	○○○○○
Brand of Probes Used:	○○○○○
Number of Temperature Probes Used:	10
Number of Relative Humidity (RH) Probes Used:	4

Internal PCDs were used for the process definition and the quantities of the PCDs placed were in compliance with ANSI/AAMI/ISO 11135-1:2007 for load volume. The appropriateness of the internal PCD was previously determined and demonstrated to be more challenging to EO sterilization than both inoculated product, when inoculated in the most difficult-to-sterilize locations, and the products natural bioburden. Comparative resistance testing was performed, in a research sterilizer, under ○○ ○○○○○○○○○○○ #○○ , #○○ Amended, and #○○ . The bioburden resistance testing was performed under NLI lab #○○ Additionally, this testing served to determine and verify the adequacy the sterilization parameters and tolerances for validation.

○○○○○
Technical Reviewer

○○○○○
Study Director

○○.○○.○○
Study Completion Date

12/35

The microbiological performance qualification (PQ) of this validation demonstrated that the sterilization process ~~delivered the specified sterility assurance level (SAL) of 10^{-6}~~ when the product and/or load combination were exposed to half of the EO process time (half cycle). Sterility of the biological indicators (BIs) was achieved during the half cycle process consisting of worse case sterilization parameters. In respects to the sterilization parameters: the preconditioning dwell time, the chamber temperature, conditioning dwell time, gas concentration, EO dwell time, and heated aeration dwell time for the half cycle processes were set below the specified routine cycle sterilization parameters (full cycle process). The lethality of the half cycle was determined using the Stumbo-Murphy Cochran (SMC) D-value equation. This method demonstrated the achievement of the required SAL for this sterilization process.

The physical PQ demonstrated that the process is reproducible and that the cycle acceptance criteria were met throughout the chamber for all phases of the cycle. The physical PQ was conducted in parallel with the microbiological PQ, by performing the full cycle process. The physical aspect of the process was confirmed as the load equilibrated near set point after preconditioning and aeration for each cycle process. The pressure rose following the emitting of gaseous EO into the chamber and was found to be within range. During EO dwell, the temperature of the chamber was found to be within range. The temperature and RH of the load during exposure were found to be acceptable. Additionally, the minimum staging time (the time it takes for the load to be pulled from preconditioning and placed into the sterilization chamber) was met. The ranges which were met, as detailed, are in respect to the cycle tolerances outlined in the half and full cycle agreements. All cycle process records were reviewed and approved by the contract sterilizer. The sponsor is responsible for the generation of acceptance criteria for routine sterilization, as determined from the evaluation of the validation load temperature and RH distribution studies.

The product validated is outlined ~~in the summary table~~. The product design and packaging configurations were determined and documented by the sponsor. The sterilant used was 100% EO. The following values and tolerances are included in the cycle process records and sterilization parameters, as provided by the contract sterilizer:

Half Cycle Process:

Preconditioning	Conditioning	EO Injection and Exposure	Aeration
Time, temperature and humidity of the chamber and load	Initial vacuum and time to achieve it	Injection pressure rise, final pressure and time	Time and temperature
Staging time	Vacuum hold time	EO gas concentration	Temperature of the product (if applicable)
Minimum temperature and humidity of load (if applicable)	Time, temperature and pressure of the chamber and load	Chamber and load temperature	Rate of air exchange (if applicable)
		Exposure time	Pressure change (if applicable)

Full Cycle Process:

Preconditioning	Conditioning	EO Injection and Exposure	Aeration
Time, temperature and humidity of the chamber and load	Initial vacuum and time to achieve it	Injection pressure rise, final pressure and time	Time and temperature
Staging time	Vacuum hold time	EO gas concentration	Temperature of the product (if applicable)
Minimum temperature and humidity of load (if applicable)	Time, temperature and pressure of the chamber and load	Chamber and load temperature	Rate of air exchange (if applicable)
		Exposure time	Pressure change (if applicable)

The purpose of this study was to address the microbiological PQ aspect of the validation and to demonstrate that the full cycle at the contract sterilizer produces product that meets the SAL requirements for a sterility claim, of at least 10^{-6}. This is the probability of one unit in a million being non-sterile and is the requirement for terminally sterilized products. The half cycle demonstrated adequate destruction of the BIs to demonstrate greater than a 12 log reduction for the full cycle and routine sterilization.

Each respective half cycle consisted of sixteen internal PCDs and one positive control for the BI lot used. The full cycle consisted of eight internal PCDs and one positive control for the BI lot used. The PCDs were used to verify the lethality of the cycle. The internal PCDs were placed adjacent to the product within the respective product boxes and included locations where sterilization was more difficult to achieve. The number of BIs used for this validation complied with ANSI/AAMI/ISO 11135-1:2007 recommendations for the specified product load volume.

For both the half and full cycles, the internal PCDs were removed from the load following the minimum set point for heated aeration.

By using the SMC equation, an approximation of the number of D_{10}s delivered by the half cycle can be calculated. (ISO 11138:2006-1: Sterilization of health care products – Biological Indicators – Part 1: General Requirements).

$$D_{10} = \frac{t}{\log_{10}(N_0) - \log_{10}\left(\ln\left(\frac{n}{r}\right)\right)}$$

Where: t = Time in minutes
N_0 = Initial spore population
n = Total number of BIs exposed
r = Number of BIs that are sterile

If: t = ○ minutes
N_0 = ○○ CFU/BI (For the BI population verified under #○○)
= ○○ CFU/BI (For the BI population verified under #○○)
n = ○○
r ○○

[a] Assumed one BI with positive growth for calculation purposes, therefore the D-value result is expressed as less than "<" the value obtained and the spore Log result is expressed as greater than ">" the value obtained.

$$D_{10} = \frac{120 \text{ minutes}}{\log_{10}(\bigcirc \text{ or } \bigcirc \times 10^6) - \log_{10}\left(\ln\left(\frac{\bigcirc}{\bigcirc}\right)\right)}$$

Then:

D-value for BIs under CRM #21930 = < ○ minutes

Therefore, a ○ minute half cycle demonstrated greater than ○ D_{10}s or greater than ○ D_{10}s per full cycle. This is greater than the twelve log reduction required for terminally sterilized products.

Additionally:

D-value for BIs under ○○ = < ○ minutes

Therefore, a 120 minute half cycle demonstrated greater than ○ D_{10}s or greater than ○ D_{10}s per full cycle. This is greater than the twelve log reduction required for terminally sterilized products.

Two loading configurations were evaluated to determine a loading configuration range. The maximum loading configuration was determined to be the worst case. This validation was performed by completing one half cycle consisting of the minimum loading configuration, and three half cycles and one full cycle consisting of the maximum loading configuration. The minimum loading configuration consisted of one shipper box, distributed over one pallet. The maximum loading configuration consisted of thirty-two shipper boxes, distributed over two pallets with sixteen shippers per pallet. The loading configurations consisted of dunnage product that was determined and provided by the sponsor. See the applicable protocol for a description of the diagrams.

The EO and ethylene chlorohydrin (ECH) residual testing demonstrated acceptable results for the product's intended use, following a 1X sterilization process, at the Day 3, Day 5 and Day 7 time points. Approximately twenty-four hours heated aeration and forty-eight hours ambient aeration was completed for the Day 3 result.

These residual results, for all time points considered, demonstrated to be below the allowable limits for the product's intended use, as a limited use device and as outlined in ANSI/AAMI/ISO 10993-7:2008 guidance document.

The temperature and RH profiles were evaluated for each loading configuration used in the half and full cycle processes. These distributions demonstrated that for the preconditioning phase, the load equilibrated. During the gas dwell phase, the product reached and maintained a temperature that demonstrated lethality with the internal BI placements. Additionally, the load was monitored during the heated aeration phase to demonstrate that the load temperature stabilized.

The number of probes used for each cycle within the sterilization load complied with the numbers outlined in ANSI/AAMI/ISO 11135-1:2007 for the respective product volume. The temperature and RH probes in the load were placed adjacent to the BIs covering all areas of the load. The temperature and RH distribution testing was completed by ○ personnel.

Revalidation should be performed approximately annually to detect any inadvertent process changes and to demonstrate that the original validation remains valid. Any changes to the product design, manufacturing facility location, packaging, loading configuration/density or to the sterilizer equipment or process should be addressed to determine the impact of the change(s) with the original validation.

The commissioning, IQ and OQ aspects of the validation are addressed by the contract sterilizer and have been previously performed. A system complying with the applicable clauses of ISO 13485 or ISO 10012 shall be specified for the calibration of all sterilization equipment. All equipment, including instrumentation for test purposes were used in meeting the requirements of this part of ISO 11135-1:2007.

Preventative maintenance of the sterilization equipment is the responsibility of the contract sterilizer and should be planned and performed in accordance with documented internal procedures.

Heat penetration studies performed to determine temperature uniformity and the most difficult to heat locations within the empty chamber are completed annually by the contract sterilizer.

Any data in regards with the maintenance, IQ and OQ are not included in this final report and it is the responsibility of the sponsor to evaluate and address this data accordingly.

This validation was based on ANSI/AAMI/ISO 11135-1:2007, "Sterilization of health care products - Ethylene oxide - Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices." These procedures are designed to ensure the validity of the sterilization process.

가-2)-② 잔류량시험 적합여부

Sterilant Gas Residue Analysis

Laboratory Number: ○○○
Test Procedure(s): Standard Test Protocol (STP) Number: ○○○○○○

Summary: All test method acceptance criteria were met.

Aeration: ○○○○○○
Date of Sterilization: ○○.○○.○○
Date Out of Forced Aeration: ○○.○○.○○
Date Into Ambient Aeration: ○○.○○.○○
Date Out of Ambient Aeration: ○○.○○.○○
Shipping Conditions: ○○○○○○
Date Into Freezer: ○○.○○.○○
Date Out of Freezer: ○○.○○.○○
Date of Extraction: ○○.○○.○○
Extraction Medium: Nelson deionized (DI) water
Analytical Analysis: Gas Chromatography (FID)

Extraction Specifics:

Extraction Type	Extraction Temperature	Extraction Time
Immersion	○○~○○℃	○○Hrs

Results:
Total Extracted Residues (mg):

Unit Number	Test Article	Number Pooled	EO		ECH	
			Pooled	Per Device	Pooled	Per Device
1	○○○○○○	○	0.511	0.170	0.210	0.070
2	○○○○○○	○	3.49	1.16	0.816	0.272
3	○○○○○○	○	0.460	0.153	<0.116	<0.039

Residual Concentrations (ppm or μg/g):

Unit Number	Test Article	EO	ECH	EG
1	○○○○○○	18.7	○○	<126
2	○○○○○○	32.2	7.54	<121
3	○○○○○○	18.4	<4.63	<139

17/35

Residual from Chromatogram (mg/L):

Unit Number	Test Article	EO	ECH	EG
1	○○○○○○	2.22	0.910	<15.0
2	○○○○○○	4.00	0.936	<15.0
3	○○○○○○	1.99	<0.5	<15.0

Note: These values are taken from the raw data and are used in the final residual concentration calculation in ppm or μg/g.

Unit Weights and Extraction Volumes:

Unit Number	Test Article	Unit Weight (g)	Extraction Volume (g)[b]
1	○○○○○○	27.41	230.56
2	○○○○○○	108.18	872.02
3	○○○○○○	24.98	231.56

[b] It is assumed that 1 gram = 1 milliliter at 20°C.

Sterilant Gas Residue Analysis

Laboratory Number: ○○○
Test Procedure(s): Standard Test Protocol (STP) Number: ○○○○○○

Summary: All test method acceptance criteria were met.

Aeration: ○○○○○○
Date of Sterilization: ○○.○○.○○
Date Out of Forced Aeration: ○○.○○.○○
Date Into Ambient Aeration: ○○.○○.○○
Date Out of Ambient Aeration: ○○.○○.○○
Shipping Conditions ○○○○○○
Date Into Freezer: ○○.○○.○○
Date Out of Freezer: ○○.○○.○○
Date of Extraction: ○○.○○.○○
Extraction Medium: Nelson deionized (DI) water
Analytical Analysis: Gas Chromatography (FID)

Extraction Specifics:

Extraction Type	Extraction Temperature	Extraction Time
Immersion	○○~○○℃	○○Hrs

Results:
Total Extracted Residues (mg):

Unit Number	Test Article	Number Pooled	EO		ECH	
			Pooled	Per Device	Pooled	Per Device
1	○○○○○○	○	0.349	○○	0.190	0.063
2	○○○○○○	○	0.395	0.132	<0.113	<0.038
3	○○○○○○	○	2.32	○○	0.612	0.204

Residual Concentrations (ppm or μg/g):

Unit Number	Test Article	EO	ECH	EG
1	○○○○○○	12.8	6.98	<123
2	○○○○○○	15.1	<4.34	○○
3	○○○○○○	21.5	5.66	<121

Residual from Chromatogram (mg/L):

Unit Number	Test Article	EO	ECH	EG
1	○○○○○○	1.56	0.849	○○
2	○○○○○○	1.74	<0.5	<15.0
3	○○○○○○	2.67	0.702	<15.0

Note: These values are taken from the raw data and are used in the final residual concentration calculation in ppm or µg/g.

Unit Weights and Extraction Volumes:

Unit Number	Test Article	Unit Weight (g)	Extraction Volume (g)[b]
1	○○○○○○	27.25	223.94
2	○○○○○○	26.11	226.47
3	○○○○○○	108.09	871.41

[b] It is assumed that 1 gram = 1 milliliter at 20°C.

Sterilant Gas Residue Analysis

Laboratory Number: ○○○
Test Procedure(s): Standard Test Protocol (STP) Number: ○○○○○○

Summary: All test method acceptance criteria were met.

Aeration: ○○○○○○
Date of Sterilization: ○○.○○.○○
Date Out of Forced Aeration: ○○.○○.○○
Date Into Ambient Aeration ○○.○○.○○
Date Out of Ambient Aeration ○○.○○.○○
Shipping Conditions: ○○○○○○
Date Into Freezer ○○.○○.○○
Date Out of Freezer ○○.○○.○○
Date of Extraction ○○.○○.○○
Extraction Medium: Nelson deionized (DI) water
Analytical Analysis: Gas Chromatography (FID)

Extraction Specifics:

Extraction Type	Extraction Temperature	Extraction Time
Immersion	○○~○○℃	○○Hrs

Results:
Total Extracted Residues (mg):

Unit Number	Test Article	Number Pooled	EO		ECH	
			Pooled	Per Device	Pooled	Per Device
1	○○○○○○	○	0.323	0.108	<0.115	<0.038
2	○○○○○○	○	0.188	0.063	0.195	0.065
3	○○○○○○	○	2.22	0.739	0.889	0.296

Residual Concentrations (ppm or μg/g):

Unit Number	Test Article	EO	ECH	EG
1	○○○○○○	14.2	<5.06	<152
2	○○○○○○	8.69	9.01	<158
3	○○○○○○	21.4	8.57	<55.8

21/35

Residual from Chromatogram (mg/L):

Unit Number	Test Article	EO	ECH	EG
1	○○○○○○	1.40	<0.5	<15.0
2	○○○○○○	0.825	0.854	<15.0
3	○○○○○○	5.75	2.31	<15.0

Note: These values are taken from the raw data and are used in the final residual concentration calculation in ppm or µg/g.

Unit Weights and Extraction Volumes:

Unit Number	Test Article	Unit Weight (g)	Extraction Volume (g)[b]
1	○○○○○○	22.74	229.97
2	○○○○○○	21.64	228.09
3	○○○○○○	103.67	385.67

[b] It is assumed that 1 gram = 1 milliliter at 20°C.

Lab ○○○ Index I
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FORM TITLE:	NUMBER
PDS / SDS / Amendment Supplemental Data Form	○○○
	REVISION: 1

Supplemental data form for: ○○○, Inc
SPONSOR: ○○○, Inc
PDS NUMBER: ○○○
REVISION: 1

SUPPLEMENTAL DATA:

1) This is an ethylene oxide (EO) validation for the different types of balloon, retriever, and catheter devices, as produced by ○○○, Inc The cycle to be validated will be cycle #○ The sterilant to be used for this validation will consist of 100% EO. The contract sterilization facility to be used for this validation is ○○○ located in Salt Lake ○○○ The chamber to be validated will be chamber #○ This validation will be based on a product load volume ≤3.8 m^3.

2) A total of four half cycles and one full cycle will be completed for this validation. A comprehensive final validation summary report will be written for all ancillary validation testing.

HALF AND FULL CYCLES

3) The half cycle cycle #○○ and full cycle cycle #○○ sterilization parameters have been recommended by ○○○○○○○○○○○○ , provided by ○○○ , and approved by ○○○. The parameters are referenced within Appendix A.

나-1)-③ 대표제품 및 BI 제시방법

LOADING CONFIGURATION

4) The maximum loading configuration to be validated will consist of thirty-two shipper boxes. The maximum loading configuration will be distributed over two pallets with sixteen shippers per pallet.

5) The minimum loading configuration to be validated will consist of one shipper box. The minimum loading configuration will be distributed over one pallet.

6) Validating a minimum and maximum loading configuration will permit ○○○ Inc. with the flexibility of sterilizing varying load volumes between this validated loading configuration range. The minimum and maximum loading configurations are referenced in Appendix B.

7) The first half cycle process will consist of the minimum or maximum loading configuration. The second half cycle process will consist of the loading configuration not evaluated during the first half cycle process. Following the completion of the two initial half cycle processes, the data generated from the temperature and relative humidity (RH) distributions of the minimum and maximum loading configurations will be evaluated to determine the worst case loading configuration. The remaining two half cycle processes will be processed using the worst case loading configuration.

23/35

FORM TITLE:	NUMBER
PDS / SDS / Amendment Supplemental Data Form	○○○
	REVISION: 1

PROCESS CHALLENGE DEVICES

8) Process challenge devices (PCDs) will be used to monitor the efficacy of the validation cycles. Multiple comparative resistance studies have been performed and reported under #○○, #○○, #○○ , and #○○ . The most recent comparative resistance study, #○○, #○○ , provided data that ○○ was more difficult to sterilize than the inoculated product, when the product was inoculated in the most difficult to sterilize locations. This validation will be performed using internal PCDs, only. ○○ will be used as the internal PCD.

BIOLOGICAL INDICATORS AND PCD PLACEMENT

9) For this validation, sixteen internal PCDs and one positive control for the BI lot will be used to monitor each respective half cycle process.

10) For this validation, eight internal PCDs and one positive control for the BI lot will be used to monitor the full and routine production cycle process.

11) ○○○○○ will place the internal PCDs throughout the validation load accordingly for each respective cycle process. The placements of the internal and/or external PCDs will be performed according to the placement map referenced in Appendix B.

12) Following the completion of heated aeration for each respective half and full cycle process, the internal PCDs will be pulled and delivered to the lab by ○○○○○ .

TEMPERATURE AND RELATIVE HUMIDITY (RH) PROBE PLACEMENT

13) For this validation, eight temperature probes and four RH probes will be placed to monitor each respective half and full cycle process. Two additional temperature probes will be placed external to the load to monitor the environmental temperature conditions of preconditioning, chamber, and aeration.

14) The placements of the temperature and RH probes will be performed by ○○ and according to the placement map referenced in Appendix B.

15) Following the completion of heated aeration of the respective half and full cycle process, the temperature and RH probes will be pulled by ○○ .

EO RESIDUALS

16) EO, ethylene chlorohydrins (ECH), and ethylene glycol (EG) residual levels will be evaluated on samples processed through a minimum of one full cycle. The sample types to be evaluated will be determined and provided by ○○○, Inc .

17) Samples processed through 1X sterilization (one full cycle) will be evaluated as follows: All product sample types, as submitted, will be evaluated at Days 3, 5 and 7. Personnel will remove nine residual samples of the new balloon product configuration as well as three residual samples of each retriever and catheter product type, following completion of heated aeration of the full cycle process.

   a) Three samples of each product type will be tested for residuals at each of the following time points: following approximately twenty-four hours of heated aeration and approximately forty-eight hours of ambient aeration for a Day 3 result, following approximately twenty-four hours of heated aeration and approximately ninety-six hours of ambient aeration for a Day 5 result, and following approximately twenty-four hours of heated aeration and approximately 144 hours of ambient aeration for a Day 7 result.

   b) If residual samples cannot be placed on test right away, the samples may be frozen until testing can be started.

18) One pre-sterilization sample, known as a "Blank" sample, of the new balloon product configuration may be evaluated for EO, ECH, and EG residuals. This will be determined by the sponsor, if testing will be completed.

19) All samples submitted for residual testing will be tested as limited use devices and will be extracted at body temperature for four hours.

20) Each test completed for this validation will be performed and reported per the respective and most recent ○ at ○ for this validation.

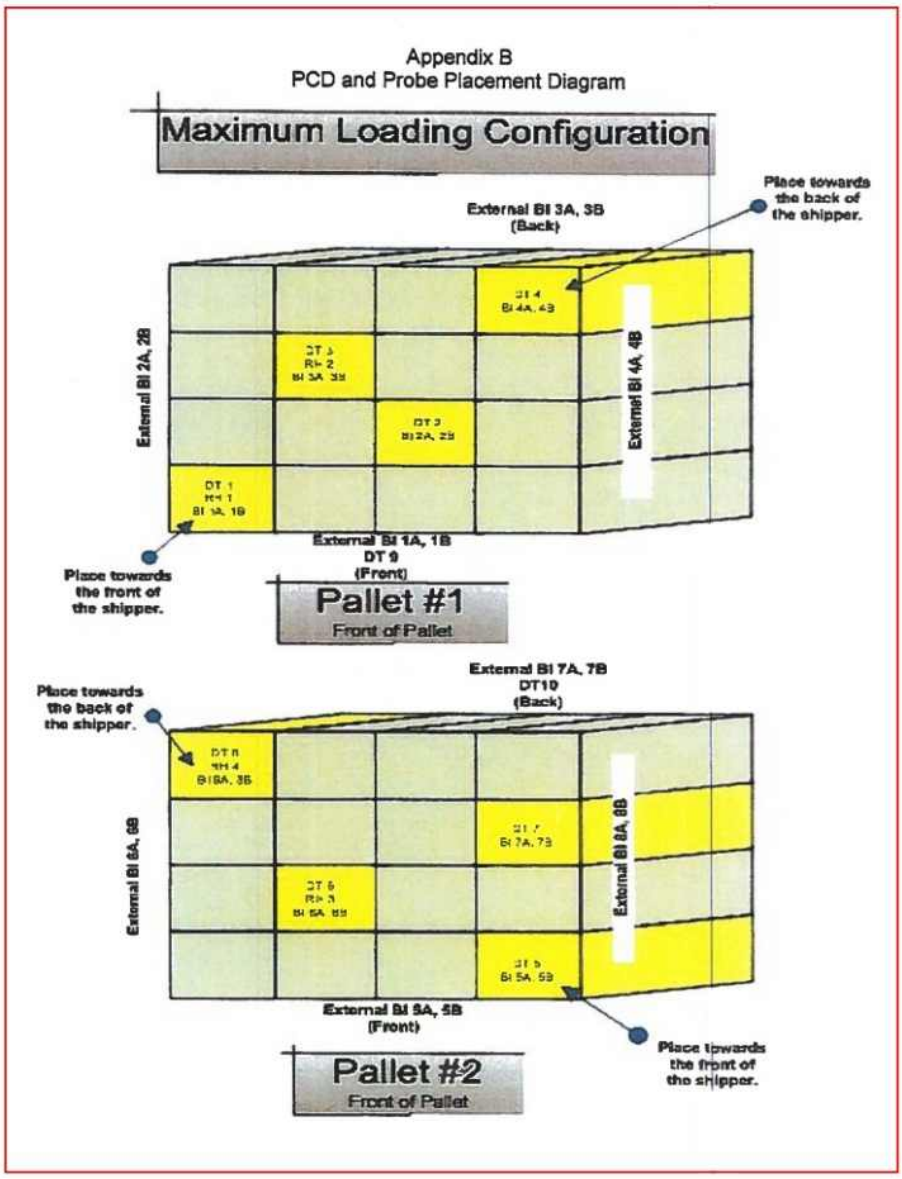
21) Test acceptance criteria is outlined within the most recent revision of the standard test procedure (STP) ○ for EO validation testing.

22) A comprehensive final summary report will be written at the conclusion of all validation testing.

Lab Number: O O O-O O

FORM TITLE:	NUMBER
oo / oo / Amendment Supplemental Data Form	O O O
	REVISION: 1

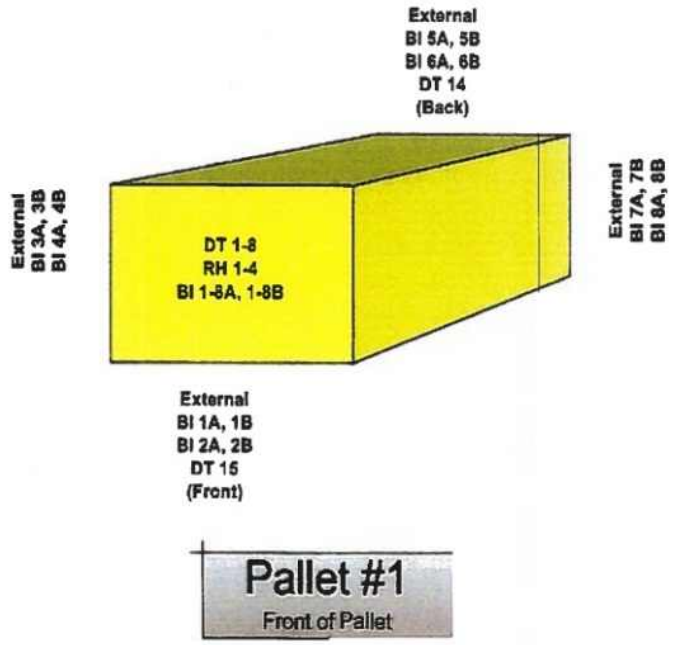
Appendix B
PCD and Probe Placement Diagram



Lab Number: ooo-oo

FORM TITLE:	NUMBER
oo / oo / Amendment Supplemental Data Form	ooo
	REVISION: 1

Minimum Loading Configuration



Note: oo temperature and RH probes will be evenly distributed throughout the load.

27/35

Comparative Resistance Study Final Report

Test Article: OOO OO
OOO OO
Purchase Order: OOO
Laboratory Number: OOO
Study Received Date: OOOO - OO - OO
Test Procedure(s): OOO

나-1)-② 대표제품 선정근거

Summary: This ethylene oxide (EO) comparative resistance study was performed to compare the resistances of the products listed above, as well as various process challenge devices (PCDs). This was completed by inoculating the test products at the most difficult to sterilize locations. The inoculated products and PCDs were then exposed to fractional sterilization cycles, following which the biological indicators (BIs) inside the PCDs and the test products were tested for sterility.

Throughout the study, the OOO devices demonstrated less resistance to EO sterilization than the OOO devices. In addition, both product types demonstrated less resistance to EO sterilization than OOO and OOO . For additional information on comparative resistance studies refer to AAMI TIR28:2009. All test method acceptance criteria were met. Further interpretation of the data is the responsibility of the sponsor and no conclusion can be made by

Results: OOO

BI Sterility Test:

Product Type	Site Description	Exposure Time in Minutes		
		120	150	180
OO	Center of the packaging hoop lumen	+,+,0	+,+,0	0,0,0
	Center of the insertion tool lumen	0,0,0	0,0,0	0,0,0
OO	Center of the packaging hoop lumen	0,0,0	0,0,0	0,0,0
	Center of the insertion tool lumen	0,0,0	0,0,0	0,0,0
	OO (direct)	+,0,0	0,0,0	0,0,0
	OO (mini spore strip)	0,0,0	0,0,0	0,0,0
	OO (direct)	+,+,+	+,+,+	+,+,+
	OO (mini spore strip)	+,+,+	+,+,+	+,+,+
	OO (direct)	+,0,0	+,+,0	0,0,0
	OO (mini spore strip)	+,+,+	+,+,0	+,0,0
	Positive Controls	+,+	+,+	+,+
	Negative Controls	0,0	0,0	0,0
	Environmental Controls	0,0	0,0	0,0

"0" = No Growth "+" = Growth

Procedure:

Product Inoculation: The test products were inoculated at four sites with a population of at least colony forming units (CFU)/site of *Bacillus atrophaeus*. The inoculation locations were as follows:

Retriever L4:
- Site #1: Center of the packaging hoop lumen (mini spore strip)
- Site #2: Center of the insertion tool lumen (direct spore suspension)

Trevo-Pro 3:
- Site #3: Center of the packaging hoop lumen (mini spore strip)
- Site #4: Center of the insertion tool lumen (direct spore suspension)

Once inoculated, the products were assembled in their original packaging configuration, which consisted of a single Tyvek® pouch inside a shelf box.

PCD Inoculation: The PCDs were inoculated with a population of at least 10^6 CFU/PCD of *B. atrophaeus*, using mini spore strips and direct spore suspension. All PCDs were assembled according to o o O O . The PCD configurations were as follows:

O O O — Consisted of approximately o/o inches of Tygon tubing with red vinyl caps placed at each end. The inoculation location was inside the Tygon tube. The o o was then sealed inside a single Tyvek® pouch.

picture1

O O O — Consisted of a o ml . Becton Dickinson (BD) syringe with approximately o/o inches of Tygon tubing placed on the luer lock with a luer adaptor. A red vinyl cap was placed at the opposite end of the tube. The o o was inoculated inside the syringe below the o ml mark and the plunger was engaged to th o-o ml mark. The o o was then sealed inside a single Tyvek® pouch.

picture2

O O O : Consisted of a o ml BD syringe with approximately two inches of Tygon tubing placed on the luer lock with a luer adaptor. A red vinyl cap was placed at the opposite end of the tube. The o o was inoculated inside the syringe below the o ml mark and the plunger was engaged to the o-o ml mark. The o o was then sealed inside a single Tyvek® pouch.

picture3

BI Population Verification: Following the receipt from the manufacturer, the mini spore strips and liquid spore suspension were tested to ensure the initial spore populations were in excess of OXO CFU/BI and OXO CFU/mL , respectively. Testing was performed according to O O O

BI Identification	NLI Verified Population	Labeled Population	Labeled D-value
O O O Exp. 02 Sep 2012	2.8 x 10^6 (CFU/mL)	2.5 x 10^6 (CFU/mL)	3.7 minutes
O O O Exp. 27 Aug 2012	1.6 x 10^6 (CFU/BI)	1.2 x 10^6 (CFU/BI)	3.9 minutes

The direct inoculations were prepared by applying O μℓ of spore suspension to each site and allowing them to dry at ambient temperature. By inoculating each site with O μℓ of spore suspension, this equates to a population of OXO CFU/site

EO Exposure: The test products and O O were sterilized in a O O model O O unit O% EO sterilizer with the following set points:

Conditioning Phase Set Points:
- Temperature: o℃
- Initial Vacuum: O O O
- Relative Humidity (RH): O O O psia
- Humidity Set Point: O O Omg/L
- Steam Dwell Time: O O Omin/second

Exposure Phase Set Points:
- Temperature: o℃
- Sterilant Set Point: O O O
- EO Concentration: O O O psia
- Gas Dwell Time: O O Omg/L
  O O Omin/second

Sterility Test: Immediately following the completion of each cycle, the BIs contained in the test products and ooo were tested for sterility by aseptically immersing them into containers of soybean casein digest broth (SCDB). The containers were then incubated at o℃ for a minimum of seven days and scored for growth of the indicator organism, *B. atrophaeus*.

The initial populations of the ooo and the test products were the same, and the samples were exposed simultaneously in the same cycles. By reducing these variables, the data can be interpreted by observing growth versus no growth to determine the resistance of the product compared to that of the ooo

나-1)-② BI선정근거

BIOBURDEN RESISTANCE STUDY

LABORATORY NUMBER: ○○○
PROCEDURE NUMBER: ○○○
PROTOCOL DETAIL SHEET NUMBER: ○○○
SAMPLE SOURCE: ○○○
SAMPLE IDENTIFICATION: Family #1: ○○○

Family #2: ○○○

Family #3: ○○○

DEVIATIONS: None
PROTOCOL APPROVAL DATE: ○○○
SAMPLE RECEIVED DATE: ○○○
LAB PHASE START DATE: ○○○
LAB PHASE COMPLETION DATE: ○○○
REPORT ISSUE DATE: ○○○

INTRODUCTION:

This ethylene oxide (EO) bioburden resistance study was conducted to compare the resistance of the validated process challenge device (PCD) to the resistance of the natural bioburden on the products listed above. The study consisted of exposing test products and PCDs to a fractional sterilization cycle. After exposure, the test products and biological indicators (BIs) contained in the PCDs were tested for sterility. A bacteriostasis/fungistasis (B/F) test was performed to validate the product sterility test. Bioburden enumeration was also performed on additional samples of each product family that had undergone all manufacturing steps up to, but not including, sterilization.

PROCEDURES:

Bioburden: Three samples of each product family that had undergone all manufacturing processes up to, but not including, sterilization were assayed for the number of aerobic bacteria and fungi present on each device. Testing was performed according to ○○○ , ○○○ standard testing protocol (STP) ○ revision (REV) ○ .

31/35

Bioburden Resistance Study

○○○
Lab Number ○○○

PCD Inoculation: The PCDs were inoculated with a population of at least 10^6 CFU/PCD of *B. atrophaeus*, using ○○○ . The PCD configuration was as follows:

○○○ : Consisted of approximately ○ inches of Tygon tubing with red vinyl caps placed at each end. The inoculation location was inside the Tygon tube. The PCD was then sealed inside a single Tyvek® pouch. See Figure 1 for a visual demonstration.

BIs: The spore strips used were manufactured by ○○ lot #○ , with an expiration date of ○.○.○ . The labeled EO D-value was ○ minutes and the labeled population was ○x○ CFU/BI.

BI Population Verification: Following the receipt from the manufacturer, the spore strips were tested to ensure the initial spore population was in excess of ○x○ CFU/BI. Testing was performed according to ○○○ REV○ .

EO Exposure: Ten test products from each family and ten PCDs were sterilized in a ○○○ Model ○ 100% EO sterilizer with the following set points:

Conditioning Phase Set Points:	
Temperature:	○℃
Initial Vacuum:	○ pounds per square inch absolute(psia)
Relative Humidity:	○%
Humidity Set Point:	○ psia
Steam Dwell Time:	○ minutes
Exposure Phase Set Points:	
Temperature:	○℃
Sterilant Set Point:	○ psia
EO Concentration:	○ mg/L
Gas Dwell Time:	○ minutes

Sterility Test: Immediately following cycle completion, the BIs contained in the PCDs were tested for sterility by aseptically immersing them into ○mL tubes of soybean casein digest broth (SCDB). The tubes were then incubated at ○-○℃ for a minimum of seven days and then scored for growth of the indicator organism, *B. atrophaeus*.

The test products were aerated overnight at ambient temperature to reduce the occupational hazard of EO gas when testing in the cleanroom. Sterility testing was performed in an ISO class five clean bench contained in an ISO class five clean room. Five samples of each product family were tested in ○mL of SCDB and incubated at ○-○℃ for ○ days The other five of each product family were tested in ○mL of fluid thioglycollate (THIO) and incubated at ○-○℃ , also for ○ days. Following incubation, all thirty test samples were scored for growth.

B/F test: In order to validate the product sterility test, a B/F test was performed. After the sterility test, nine containers of SCDB containing the test product (three of each product family) were inoculated with not more than 100 organisms of *Bacillus subtilis*, *Aspergillus niger*, and *Candida albicans*. These samples were incubated at ○-○℃ for not more than five days. Nine containers of THIO containing the test product (three of each product family) were inoculated with not more than 100 organisms of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Clostridium sporogenes*. These samples were incubated at ○-○℃ for not more than five days. The samples were then checked for growth and released after incubation. The volume of media used for the B/F test was the same volume that was used for the product sterility test. Positive controls (containers of media without the test product) were also inoculated and incubated as described above.

RESULTS:

The population of the ○○○ lot○ , was verified to be 3.5 x 10^6 CFU/BI.

The bioburden enumeration results are summarized in Table 1.

The BI sterility test results of the PCDs are summarized in Table 2.

The product sterility test results are summarized in Table 3.

The B/F test results are summarized in Table 4.

CONCLUSION:

Throughout the study, the naturally occurring bioburden on the test products demonstrated to be less resistant to EO sterilization than the validated PCDs. Furthermore, the B/F test showed that the products are not bacteriostatic or fungistatic. For additional information on bioburden resistance requirements, refer to ANSI/AAMI/ISO 11135-1:2007.

Lab Number ○○○

Further interpretation of the data is the responsibility of the sponsor and no conclusion can be made by ○○

STATEMENT OF UNCERTANITY:

If applicable, the statement of uncertainty is available to sponsors upon request.

○○○

Technical Reviewer

○○○

Study Director

○○○

Study Completion Date

Endotoxin Analysis Certificate

Test Sample	○○○
Test Facility	○○○
Date of testing conducted	○○○
Test Reagent	
Endotoxin	Manufacturer: ○○○ Lot Number: ○○○ Expiration Date: ○○○ EU/ng ratio: ○○ Date Reconstituted: ○○○
LAL	Manufacturer: ○○○ Lot Number #: ○○○ Expiration Date: ○○○ ○ EU/ml ○○○
Referenced Endotoxin Test Standard	USP ○○○
Test Method	Lead is extracted in sterile water ○ ml/device for ○ hour at room temperature ○-○℃ or ○ minutes ○℃ (in an incubator shaker). Then test the Pooled Device Extract per LAL gel-clot procedure.
Results	○ EU/device
Conclusion	Bacteria endotoxin is measured in Endotoxin Units (EU). Detected EU was less than ○ EU/device Therefore, compliance with Medtronic requirement is achieved.

라-1)-① 시험기준 선정

라-1)-① 엔도톡신 시험 방법 설명

라-1)-① 시험기준 충족여부

Date: ○○○

Signature: ○○○

Name: ○○○

Title: ○○○

35/35

협의체 위원

연번	기관(협회)명	직급	성명	비고
1	한국산업기술시험원	선임연구원	공석경	시험검사기관
2	한국화학시험연구원	과장	이승영	시험검사기관
3	세원셀론텍(주)	차장	유지철	제조업체
4	㈜제노스	주임	홍기택	제조업체
5	㈜코렌텍	차장	성정현	제조업체
6	한스바이오메드(주)	이사	임홍열	제조업체
7	메드트로닉코리아(유)	차장	박지윤	수입업체
8	㈜바이오메트코리아	대리	전신영	수입업체
9	한국스트라이커(주)	대리	손경민	수입업체
10	한국엘러간(주)	과장	단인호	수입업체
11	한국존슨앤드존슨메디칼(주)	과장	최일우	수입업체

의료기기 무균 입증 자료에 관한 가이드라인

발 행 처	식품의약품안전처 식품의약품안전평가원 의료기기심사부
발 행 일	2014년 11월
발 행 인	왕진호
편집위원장	정희교
편 집 위 원	조양하, 박기정, 이정림, 윤미옥, 오현주, 이인수, 허찬회, 정진백, 강영규, 이원규, 이수해, 정승환, 성홍모, 박해대, 김수연, 양승하, 고동현, 류지혜, 추성욱, 배영우, 양원선, 이웅태, 정아름, 강건우, 김명옥, 구상모, 홍미애, 김다영
문 의 처	(363-951) 충북 청주시 흥덕구 오송읍 오송생명5로 303 식품의약품안전처 별관 국도푸르미르빌딩 5층 의료기기심사부 정형재활기기과 전화 : 043-230-0554~0559 팩스 : 043-230-0550