의약품 순도기준 규격 합리화 방안
: 완제의약품 중 이성체 규격 설정

1 검토배경

❍ 원료의약품이 광학이성체인 경우,

→ 원료의약품 : 의약품등의 품목허가·신고·심사규정 제7조 및 제33조에 따라 **이성체에 관한 자료** 및 **목적하지 아니한 이성체에 대하여 순도시험에 기준 및 시험방법을 설정**하도록 하고 있으나,

→ 완제의약품의 검토 기준에 대한 상세 지침이 없음

2 심사개선방안

❍ 원료의약품이 광학이성체인 경우,

1) 완제의약품의 제조공정 및 보관 중 **이성체순도에 대한 자료를 검토하여** (시험성적 및 안정성시험자료)

→ **유의적인 변화가 일어나지 않는 경우 : 완제의약품의 이성체순도 기준 및 시험방법 미설정**

예) **안정성시험 결과, 완제의약품의 이성체 순도가 원료의약품 기준치를 초과하지 않고, 원료측정치를 기준으로 완제의약품에서 시간에 따라 증가하는 경향을 보이지 않을 때 등**

※ 참고자료

1. 의약품등의 품목허가·신고·심사규정

제7조(심사자료의 요건)

2. 구조결정·물리화학적 및 생물학적 성질에 관한 자료(품질에 관한 자료)

나. 원료의약품에 관한 자료

2) 물리화학적 성질에 관한 자료

차) 이성체(광학이성체 등) : 원료의약품이 광학이성체 등 이성체의 혼합물인 경우에는 이성체의 분리·분석법에 관한 자료 및 이성체비에 관한 자료

다. 완제의약품에 관한 자료

4) 기준 및 시험방법에 관한 근거자료

나) 순도시험에 관한 자료

(1) 일반적 사항은 원료의약품의 순도시험에 관한 자료에 따른다.

제33조(원료의약품의 기준 및 시험방법 자료의 작성)

③ 원료의약품 별첨규격 작성항목은 다음 각호에 따라 순서대로 기재한다.

9. 순도시험

마. 이성체가 분리된 원료의약품의 경우 목적하지 아니한 이성체에 대하여 설정하여 기재한다.

제34조(완제의약품의 기준 및 시험방법 자료의 작성)

③ 기준 및 시험방법은 다음 각 호에 따라 순서대로 기재한다.

4. 순도시험

나. 제제화 과정 또는 보존 중에 변화가 예상되는 경우에 설정한다.

2. EMEA 가이드라인 : Investigation of Chiral Active Substances

4. QUALITY ASPECTS

Finished product

It should be demonstrated and supported by validated test procedures, that during the manufacturing process of the finished product no unacceptable change in stereochemical purity or ratio of the active substance occurs.

Stability

It should be demonstrated for both the raw material (active substance) and finished product that, within the specifications, no unacceptable change in stereochemical purity or ratio occurs during the proposed shelf-life.

3. ICH 가이드라인 Q6A

- Specification : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products : Chemical Substance

d) Tests for chiral new drug substances: Where a new drug substance is predominantly one enantiomer, the opposite enantiomer is excluded from the qualification and identification thresholds given in the ICH Guidelines on Impurities in New Drug Substances and Impurities in New Drug Products because of practical difficulties in quantifying it at those levels. However, that impurity in the chiral new drug substance and the resulting new drug product(s) should otherwise be treated according to the principles established in those Guidelines.

Decision tree #5 summarizes when and if chiral identity tests, impurity tests, and assays may be needed for both new drug substances and new drug products, according to the following concepts:

Drug Substance: Impurities. For chiral drug substances which are developed as a single enantiomer, control of the other enantiomer should be considered in the same manner as for other impurities. However, technical limitations may preclude the same limits of quantification or qualification from being applied. Assurance of control also could be given by appropriate testing of a starting material or intermediate, with suitable justification.

Assay. An enantioselective determination of the drug substance should be part of the specification. It is considered acceptable for this to be achieved either through use of a chiral assay procedure or by the combination of an achiral assay together with appropriate methods of controlling the enantiomeric impurity.

Identity. For a drug substance developed as a single enantiomer, the identity test(s) should be capable of distinguishing both enantiomers and the racemic mixture. For a racemic drug substance, there are generally two situations where a stereospecific identity test is appropriate for release/acceptance testing: 1) where there is a significant possibility that the enantiomer might be substituted for the racemate, or 2) when there is evidence that preferential crystallization may lead to unintentional production of a non-racemic mixture.

Drug Product: **Degradation products.** **Control of the other enantiomer in a drug product is considered necessary unless racemization has been shown to be insignificant during manufacture of the dosage form, and on storage.**

Assay: An achiral assay may be sufficient where racemization has been shown to be insignificant during manufacture of the dosage form, and on storage. Otherwise a chiral assay should be used, or alternatively, the combination of an achiral assay plus a validated procedure to control the presence of the opposite enantiomer may be used.

Identity: A stereospecific identity test is not generally needed in the drug product release specification. When racemization is insignificant during manufacture of the dosage form, and on storage, stereospecific identity testing is more appropriately addressed as part of the drug substance specification. When racemization in the dosage form is a concern, chiral assay or enantiomeric impurity testing of the drug product will serve to verify identity.