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Lääkealan turvallisuus- ja kehittämiskeskus | Säkerhets- och utvecklingscentret för läkemedelsområdet | Finnish Medicines Agency

Session 2: Guideline on Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues

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Biosimilar quality guideline

- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues
  - Drafting group formed in 2004
  - Draft release for consultation in March 2005
  - CHMP adoption in Feb 2006
- Revision 1
  - Drafting group formed in 2011
  - Draft release for consultation in May 2012 (EMA/CHMP/BWP/247713/2012)
  - End of consultation: November 2012
  - Comments received from 14 stakeholders

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Quality guideline; Manufacturing process

- Quality Target Product Profile (QTPP):
  - ICH Q8: A prospective summary of the quality characteristics of a drug product that ideally will be achieved..
  - Primarily based on extensive characterisation data collected from the reference medicinal product
  - Detailed at an early stage of development and forms the basis for the development of the biosimilar product and its manufacturing process.
- The expression system should be carefully selected considering its impact on the safety and/or efficacy profile of the biosimilar
  - E.g., novel expression systems may introduce additional risk, such as atypical glycosylation pattern

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Quality guideline; Manufacturing process

- Acknowledgment of own lifecycles
  - Changes to the manufacturing process: ICH Q5E
  - Addressed separately from the comparability exercise versus the reference
- Advisable to generate the required quality, safety and efficacy data for the biosimilar comparability study with product manufactured with the final manufacturing process and therefore representing the quality profile of the batches to be commercialised
- Formulation: does not need to be identical
- The stability of the biosimilar should be determined according to ICH Q5C

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Quality guideline; Comparability exercise

- An extensive comparability exercise required
  - Assessment of composition, physical properties, primary and higher order structures, purity, product-related isoforms and impurities, and biological activity
  - Target amino acid sequence should be confirmed and is expected to be the same as for the reference product
- The desired product and product-related substances present in the finished product of the biosimilar should be highly similar to that of the reference medicinal product
  - It may be very challenging to claim biosimilarity if significant quality differences are confirmed (e.g. atypical post-translational structures with impact on safety or efficacy)

Quality guideline; Comparability exercise

- Target acceptance criteria:
  - Quantitative limits should be justified taking into account the number of reference medicinal product lots tested, the quality attribute investigated and the test method used
  - Should not be wider than the range of variability of the representative reference medicinal (unless otherwise justified)
  - Acceptance criteria used for the comparability exercise versus the reference medicinal product should be handled separately from release specifications (which are established in accordance with ICH Q6B)

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Quality guideline; Comparability exercise

- Shift in quality profile of reference product
  - Reference product may evolve through its lifecycle.
  - Could occur during development of a biosimilar product and may result in a development according to a QTPP which is no longer fully representative of the reference product on the market
  - Usually acceptable to use both pre- and post-change ranges
- Monoclonal antibodies or related substances – immunological properties should be fully compared
  - Affinity to the intended target
  - Binding affinity of the Fc to relevant receptors
  - Ability to induce Fab- and Fc-associated effector functions

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Summary of main comments

- Clarification requested on how to apply QTPP concept
- Further clarity requested on the use of different/ novel expression systems
- Terminology – Comparability vs. Biosimilarity
- Clarification requested on appropriate use of publicly available standards (especially Ph. Eur. Standards)
- Global development – further details requested
- Further clarity requested regarding acceptable differences
- CTD requirements (location of the quality comparability exercise)