Regulatory Consideration for Biosimilar Products

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Outline

- KFDA activities related to Biosimilar products
- Requirements for approval of Biosimilar Products
  - Principles of Biosimilar Approach
  - Requirements for Quality studies
  - Requirements for Non-clinical studies
  - Requirements for Clinical studies
- Issues & Suggestions
KFDA Activities related to Biosimilars

- 2007.4. Discussion group was established
- 2008.5. FDA/WHO Joint Symposium on Biosimilar Products
- 2009.7. Guideline on Evaluation of Biosimilar Products
  Regulation on Marketing Authorization of Biopharmaceutical Products”, amended
- 2010.8. KFDA/WHO Joint Workshop on Implementation on WHO Guideline on Evaluating Similar Biological Products
What is Biosimilars?

- **Definition**
  - a biotechnological product that *is proved to be comparable to an already approved reference product* in quality, non-clinical and clinical evaluation

- **Scope**
  - well-characterized recombinant protein products
    - EMEA : All biologics
    - Japan : Recombinant Vaccines
      - Recombinant plasma proteins
Regulatory perspectives for Biosimilar Products

• Existing generic definition is not appropriate for biosimilar

• Approval of the biosimilar product should be based on the demonstration of similarity to a suitable reference drug with comprehensive comparative data

• Comprehensive characterization and comparison at quality level shall provide a basis for a reduction in the non-clinical and clinical data

• A final determination of similarity can be based on a combination of quality, non-clinical and clinical evaluation
# Dossier Requirements for Approval

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Reference Drug

• The reference drug should be already approved on the basis of a complete dossier package in Korea

• The reference drug should be used throughout the studies supporting the quality, safety, and efficacy of the product

• The dosage form, strength, and route of administration of the biosimilar product should be the same as that of the reference product

• The biosimilar product should not be used as a reference drug
Requirements for Quality studies

- Full CMC and comparability exercise data between biosimilar product and reference product are required
  - Extensive side by side characterization
  - Physicochemical properties (including Immunochemical properties)
  - Biological activity
  - Specification
  - Impurities
  - Stability

✓ Analytical techniques should be state of art to detect slight differences in quality attributes
✓ Acceptance criteria in setting up the specification should be established and justified based on the results of a number of representative lot analyses
Demonstration of Similarity

- The demonstration of comparability does not necessarily mean that the quality attributes of the two products will be identical, but they are highly similar with two consequences.

- Minor structural differences such as variability in post-translational modifications may be acceptable but must be justified.

- Differences in impurity profiles should be justified.

- The impact of observed differences in the quality attributes should be assessed and then non-clinical and clinical studies should be designed and conducted on the basis of the results.
Requirements for Non-clinical Studies

- **Comparative non-clinical studies** should be designed to detect significant differences between the biosimilar product and the reference product
  
  - *In vitro study*
    - Receptor binding study
    - Cell proliferation assay
  
  - *In vivo study*
    - Biological/Pharmacodynamic studies relevant to the clinical application
  
  - **Toxicity**
    - At least one repeat dose toxicity study in a relevant species, including toxicokinetic study, antibody measurement
Requirements for Clinical studies

- Comparative clinical trials are required depending on the data in terms of quality and nonclinical studies.
  - Pharmacokinetic Studies/Pharmacodynamic Studies
  - Clinical Efficacy & Safety trials
  - Confirmatory PK/PD studies

- Equivalence trial is preferable, and margins should be pre-specified and justified

- Extrapolation to other indications of the reference drug may be possible if similar efficacy and safety established in a ‘sensitive’ test model and scientifically justified

- Pre-approval safety data from sufficient number of patients and study duration should be provided to compare the nature, severity, and frequency of adverse reactions (including immunogenicity study)
Issues on clinical evaluation

- Treatment practices with reference product may have changed and effect on clinical study design and recruitment
- Choice of appropriate clinically relevant endpoints is important
- Cross-over studies may not be appropriate for protein therapeutics with a long half-life
- Patient population may affect sensitivity; adequate population to detect a clinically meaningful difference
- Setting a relevant similarity margin; equivalence trials may need to be very large.
- There is a need to build capacity for expertise; clinical and statistical consideration.
Issues on clinical evaluation

- **Reference drug**
  - Need to prevent duplication of clinical studies in each region

- **Extrapolation of indication**
  - Need to have more a comprehensive and accurate approach to specify which data are based on extrapolation.

- **Interchangeability**
  - Currently, no clinical studies have been undertaken to assess clinical outcomes or repeated switches of a biologic product

- **Post-Marketing pharmacovigilance**
  - Pre-approval clinical safety data are insufficient to identify all the potential safety profiles; immunogenicity
Suggestion for Biosimilar Products

- Global harmonization on scientific basis for decision making
- Collaboration on information sharing; database for regulatory information
- Collaboration on capacity building for expertise; clinical and statistical consideration
- Collaboration on post-market surveillance for patient safety
Conclusions

- Biopharmaceuticals are different from small molecule chemical drug
- Generic drug approval approach is not appropriate
- Establishing a high degree of similarity in quality between the biosimilar product and the original product is a crucial key in the regulatory approval process
- The development of the biosimilar products is complex and there is a need for a consistent and efficient global approach, in order to expand global access to safe and effective biological medicines
Thank you for attention!