Biosimilar regulation in Republic of Korea and Asia-Pacific Economic Cooperation (APEC) developments

Outline

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Korean Regulatory Framework for Biosimilar Products

Legislative basis of biosimilar products approval in Korea

- **Legislative basis for regulating biosimilar products** was established in September, 2009, which was reflected in Ministry of Food and Drug Safety (MFDS) Notification

- ‘Guideline on Evaluation of Biosimilar Products’ and ‘Questions & Answers regarding Biosimilar Guideline’ were issued in September, 2009
  - These guidelines are being revised in 2014 to reflect current thinking of MFDS
Product specific guidelines

Product specific guidelines are being published annually

- Guideline on non-clinical and clinical evaluation of erythropoietin and somatropin biosimilar products (2011)
- Guideline on non-clinical and clinical evaluation of monoclonal antibody biosimilar products (2013)

Principles of the biosimilar approach

- The approval of biosimilar products should be based on the demonstration of similarity to a chosen reference product
- The comprehensive characterization and comparison at quality level should provide a basis for a reduction in the non-clinical and clinical data
- Regulatory decision making should be based on a comprehensive evaluation of quality, safety and efficacy data
Definition & Scope of biosimilar product

• 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

Reference products

• Reference products should be already approved on the basis of a complete dossier package in Korea

• Reference products should be used throughout the studies supporting the quality, safety, and efficacy of the products

• Use of non-Korean (out-sourced) reference products may be acceptable, provided that sufficient information to justify the comparability to Korean reference products would be demonstrated
Requirements for quality studies

• Full quality dossier and comparability exercise data between biosimilar products and reference products are required

  ✓ Comparability: extensive side-by-side characterization

• Justification of acceptance criteria used in the comparability taking into account the sufficient number of reference products lots tested is important

• The impact of observed differences in the quality attributes should be assessed

Requirements for non-clinical studies

• Comparative non-clinical studies should be designed to detect significant differences between biosimilar products and reference products

  - In vitro study
    • Receptor binding study, Cell based bioassay
  - In vivo study
    • Biological/Pharmacodynamic studies relevant to the clinical application

  - Toxicity
    • At least one comparative repeated-dose toxicity study in relevant species, including toxicokinetic study, anti-drug antibody measurement
Requirements for clinical studies

- Comparative clinical trials are required
  - Pharmacokinetic studies/Pharmacodynamic studies
  - Clinical Efficacy & safety trials
  - Confirmatory PK/PD studies

- Equivalence design is recommended and equivalence margins should be pre-specified and justified

- 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) before approval

Extrapolation of indications

- Sufficient safety and efficacy information should be provided for each indications of the reference product to extrapolate the indications of a biosimilar product

- The extrapolation of clinical indications of a biosimilar product is allowed, if all of the following conditions are fulfilled;
  - Sensitive clinical model to detect potential differences are used
  - Clinically relevant mechanism of action and involved receptor are same in different indications
  - Safety and immunogenicity have been sufficiently characterized
Interchangeability

• Unlike chemical generic products, **automatic substitution of biosimilar products is not allowed** in Korea

Pharmacovigilance

• Generally, clinical safety data from pre-authorization studies are insufficient to identify all potential safety profiles

• **4 year post-marketing surveillance (PMS)** of a biosimilar product on the safety and efficacy profile is required

• The **PMS study plan** should be submitted to MFDS **before marketing** of a biosimilar product

• The findings obtained from the PMS study should be reported to MFDS periodically
**Status of Biosimilar development in Korea (1)**

- **15 biosimilar candidates with 23 protocols (as of 2013)**
  - 9 local manufacturers, 2 global companies
  - 15 phase 1 trials, 8 phase 3 trials

![Bar chart showing No of IND from 2009 to 2013](chart.png)

**Status of Biosimilar development in Korea (2)**

- **Popular reference products**
  - Trastuzumab, Etanercept, Infliximab, Rituximab

- **2 Korean biosimilar products authorized**
  - Remsima (Infliximab, '12.7.20)
  - Herzuma (Trastuzumab, '13.1.15)
Issues and Challenges in Biosimilar Approval

In case that a relevant animal model dose not exist
- Toxicity studies in non-relevant species may not demonstrate meaningful difference
- Study using transgenic animals only demonstrates supportive outcomes due to variability

⇒ No animal data needed before human trial?
Sensitive population

- Sensitive populations for PK, efficacy, safety (immunogenicity) are not always same
- Considerations
  - Sufficient experience as medical practice
  - Magnitude of treatment effect
  - Dosing regimen, combination/mono therapy
- Strategies in designing of clinical studies are important with respect to extrapolation of indications

Clinical Endpoint

- The purpose of clinical study of biosimilar is to demonstrate similarity to the reference product
- Sensitive endpoint to detect differences
e.g. OS/PFS are traditional anti-tumor endpoints for new drugs but maybe not suitable for biosimilars
- Selection of endpoint and time point for evaluation should be justified
- Traditional endpoint should be included as a secondary endpoint
Efforts on biosimilar regulatory convergence in APEC

- APEC biotherapeutic roadmap -

APEC Roadmap for Biotherapeutic Products

- Initiated to create the roadmap in line with LSIF (Life Sciences Innovation Forum) strategic plans for the convergence of approaches to the regulation of biological products in APEC economies (Sep 2011, APEC SOM Meeting)
  - Korea was designated ‘champion nation’ to establish the roadmap
- The Roadmap for Biotherapeutic Products was officially endorsed at RHSC meeting (Feb. 2013)
**Regulatory convergence in APEC economies by 2020**

- **Step 1**: 2013~2014
  - Assessment by workshop

- **Step 2**: 2014~2018
  - Training & Workshop

- **Step 3**: 2018~2019
  - Assessment for training/workshop

- **Step 4**: 2019~2020
  - Training/workshop to reach goals and recommendations for regulatory convergence to RHSC

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**AHC Biotherapeutics Workshop**

- AHC biotherapeutics (and biosimilar) workshop is a tool for accomplishing the ‘Roadmap for biotherapeutic products’ to member economies
- Areas of regulatory convergence in biosimilar (2012) and biotherapeutics (2013) were discussed in the Workshop which is being organized in Seoul, Korea annually
- Workshop conclusions and recommendations will be reflected to the Roadmap for lively revision
- Work sharing with WHO and IPRF will be the next agenda for AHC
(Proposed) **Areas of convergence**

- Biosimilars are not generics
- Scientific principles should drive development and complement WHO guideline
- Single reference product should be used
- Step-wise approach should be adopted for evaluation
- Agency consultation is encouraged, tailored to biosimilar mindset
- Regulatory convergence supports simultaneous global development
- Post-marketing surveillance is essential

(Proposed) **Opportunities for convergence**

- Interchangeability and the methods to achieve it
- Applications of immunogenicity
- Many areas open for interpretation without common language and principle
- Limitations in existing PMS systems and applications to biosimilars (e.g. naming)
- Extrapolation of indications
- Impact of post-marketing manufacturing changes
- Acceptance criteria of foreign reference products or list of recognized reference products
MFDS work sharing with other regulators for convergence

- WHO Collaborating Center
  - Support for development and implementation of WHO SBP and biotherapeutics guidelines

- International Pharmaceutical Regulators Network
  - Created ‘Biosimilar Working Group’ in 2013.11
  - Members; 32 regulators form 10 countries and 3 international organizations (Chair: Korea)

- Bilateral discussions between NRAs
  - MFDS has been organizing ‘Biosimilar Review Workshop’ with regulators from Japan (‘12), Canada (‘13) and Germany (‘14.8)

Conclusion

- Biosimilar regulation poses a number of substantial scientific and regulatory challenges for regulatory authorities
- Demonstration of high degree of similarity between biosimilar and reference products is a crucial key in the regulatory approval process
- Strategies in developing biosimilar products will be important
- Global alliance in sharing information will be of value for biosimilar products regulatory convergence