Regulatory development of Biosimilars in Republic of Korea and IPRF Biosimilars Working Group Activities
29 April 2016
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2. Issues and Challenges in Biosimilar Approval
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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 have been revised in 2014 to reflect current thinking of MFDS
Product specific guidelines

Product specific guidelines are being published

• Guideline on non-clinical and clinical evaluation of erythropoietin and somatropin biosimilar products (2011)

• Guideline on non-clinical and clinical evaluation of G-CSF biosimilar products (2012)

• Guideline on non-clinical and clinical evaluation of monoclonal antibody biosimilar products (2013)

• Guideline on non-clinical and clinical evaluation of insulin and insulin-analog biosimilar products (2015)

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
    • **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 Biosimilars development in Korea

• Popular reference products
  ✓ Adalimumab, Infliximab, Etanercept, Rituximab, Trastuzumab

Status of Biosimilars development in Korea

• 21 Biosimilar candidates (as of 2015)
  ✓ 12 domestic products, 9 global products

• 4 Korean biosimilar products authorized
  ✓ Remsima (Infliximab, ‘12. 7.20)
  ✓ Herzuma (Trastuzumab, ‘13. 1.15)
  ✓ Benepali (Etanercept, ‘15. 9. 7)
  ✓ Flixabi (Infliximab, ‘15.12. 4)
Issues and Challenges in Biosimilar Approval

Issues and Challenges

- **Quality**
  How similar? Statistical approach?

- **Non-clinical**
  No animal data before clinical trial?

- **Clinical**
  Sensitive population? Sensitive design?
  Equivalence margin? Extrapolation?

- Reference products
- Immunogenicity?
- Biosimilars for rare disease?
Efforts on Biosimilar Regulatory Convergence in IPRF Biosimilar Working Group

IPRF Biosimilars Working Group

[International Pharmaceutical Regulators Forum (IPRF) BWG]

- **Initiated**: Nov. ‘13
- **Mandate confirmed**: Jun. ‘14
- **Representation**: 32 Global Regulators from 11 countries and 3 international organizations
- **Chair/ Co-chair**: MFDS/EMA
- **Objective** - For regulatory convergence of technical requirements
  - To support int’l regulators develop frameworks for Biosimilars
- **Operation**: one F2F meeting and three t/cs /year since 2014
IPRF Biosimilars Working Group

[International Pharmaceutical Regulators Forum]

BWG Focus on

1. Public Assessment Summary Information for Biosimilar (PASIB)
2. Reflection Paper for extrapolation of indications

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1. PASIB_Intention

- **Information sharing tool**
  - A summary of assessment of biosimilar application with ONE language (English) to be accessed by global community

- **Increasing transparency**
  - To facilitate the transition from a local assessment report to one prepared in the English

- **Use of common template**
  - To reduce local translation effort by competent authority which doesn’t use English

1. PASIB_Template

- Consisted with **three parts**
  - Part A: Administrative information
  - Part B: Submitted data and reviewer’s summary
  - Part C: Reviewer’s conclusion
1. PASIB_Documents for feedback

- The documents at this stage are comprised of a
  - template
  - template information
  - four completed examples:
    – Remsima (EMA & MFDS)
    – Zarzio (EMA)
    – Herzuma (MFDS)

- Posted at IPRF website (http://www.i-p-r-f.org)
- Looking forward to feedback by 9 May 2016

2. Reflection Paper

- Survey conducted among BWG members (2015) and topic selected as Extrapolation of indication

- Investigational study has been done to understand
  – What are the recommendations for extrapolation of indications? (comparison of guidelines)
  – How extrapolation of indications was concluded based on assessment? (comparison of assessment reports)
  – What are the critical aspects clinical studies to have extrapolation of indications? (comparison of clinical design)
2. Reflection Paper

- This document is proposed to reflect BWG members’ consideration on extrapolation of indications of biosimilar products

- The contents of reflection paper
  - How to demonstrate same mechanism of action and same receptor with reference product
  - What are sensitive models for clinical designs (considerations by product class)

2. Reflection Paper

- How to conclude extrapolation of indication from totality of evidence
- Role of quality & nonclinical data in providing assurance for extrapolation

- Draft of reflection paper has been finalized and published through IPRF website by 3Q 2016 after discussion with IPRF secretariat
3. Manual for Regulatory Reviewers

- Survey conducted among BWG members (2015) and another topic selected as **Analytical comparability**
- Co-development of “**Manual for Regulatory reviewers**: Analytical comparability of biosimilar monoclonal antibodies” with WHO
- The target for the material should be CMC reviewers who have experience with rDNA products.

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3. Manual for Regulatory Reviewers

- The contents will include the
  - General consideration
  - Product quality in development of biosimilars
  - Biosimilarity
  - Critical quality attributes for analytical comparability of monoclonal antibodies
  - Determination of similarity
  - Analytical comparability and potential impact on extrapolation
  - Case study
3. Manual for Regulatory Reviewers

• Drafting of manual will be made during BWG F2F meeting in June 2016
• Publication at IPRF and WHO Website: End of 2016
  – Publication will be through IPRF Website after discussion with IPRF secretariat

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
good luck

Thank you!
감사합니다