Regulatory Framework on Biosimilar in Korea

Baek, Kyung-min

Recombinant Protein Products Division

Ministry of Food and Drug Safety
● About Ministry of Food and Drug Safety
● Regulation for Biosimilar
● Principle of Biosimilar Approach
● Status of Biosimilar development in Korea
About Ministry of Food and Drug Safety
Vision of MFDS

**Vision**

*Safe Food and Drugs, Healthy Nation, Well-being of Society*

1. Ensuring safety of the people to improve quality of life
2. Consumer-based safety management from Farm to Table
3. Realization of safer and healthier lives of the people
4. Beyond safety, providing assurance to the people

**Core Strategies**

- Eradication of adulterated foods
- Coherent safety management from Farm to Table
- Promotion of consumer participation and increase in consumer awareness for safety
- Creation of job opportunities
- Rapid release of medical products
- Virtuous circle of safety and industrial development
- Close collaboration with healthcare policy

*MINISTRY OF FOOD AND DRUG SAFETY*
Structure of MFDS

● Organization elevated status by revision on the “Government Organization Act” (2013.03.22.)
  ◦ Korea Food and Drug Administration
    ➞ Ministry of Food and Drug Safety

● To consolidate food management system, organization is restructured and expended
  ◦ Now includes agricultural, livestock and fishery products
as of April, 2013
- 1 headquarter, 6 regional offices
- 1 affiliated institute (NIFDS)
- 13 Imported Food Inspection Centers
- Total number of employees: about 1,700
Biopharmaceutical related Divisions

- In Headquarter
  - Biopharmaceuticals and Herbal Medicine Bureau
  - Biopharmaceutical Policy Division
    - Marketing authorization
    - Policy, Law & Regulations
  - Biopharmaceutical Quality Management Division
    - GMP compliance
    - PMS
In NIFDS (National Institute of Food and Drug Safety Evaluation)

- Biopharmaceuticals and Herbal Medicines Evaluation Department
  - Biologics Division
    - Vaccines, Blood derived products
  - Recombinant Protein Products Division
    - DNA recombinant Products
  - Cell and Gene Therapy Products Division

Review submitted BLA (Quality, Safety & Efficacy)
Review Clinical Protocols / Establish Guideline
- Pharmaceutical and Medical Device Research Department
  - Biopharmaceuticals and Research Division
    - Vaccine, Blood derived products related R&D
    - Review and testing of method of Vaccine, Blood derived products
  - Advanced Biopharmaceutical Products Division
    - DNA recombinant product, Cell and Gene therapy product related R&D
    - Review and testing of method of Recombinant product, Cell and Gene therapy product
• Regulation for Biosimilar
Legislative Basis for Regulation

- **The Pharmaceutical Affairs Act (PAA)**
- **Enforcement Regulation of the PAA**
  - Good Manufacturing Practice for Biologics
  - Enforcement Decree on the Standards of Facilities of Pharmacies and Manufacturers, Importers and Distributors of Drugs, etc.
- **Notifications**
  - Regulation on Review and Authorization of Biological Products
  - Regulation on Drug Safety Information Management (Pharmacovigilance system)
  - Korean Minimum Requirements for biologics
- **Guidelines**
Legislative basis for regulating biosimilar products was established in September, 2009, which was reflected in MFDS Notification, “Regulation on Approval and Review of Biopharmaceutical Products”

“Guideline on Evaluation of Biosimilar Products” and “Questions & Answers Regarding Biosimilar Guideline” were issued in September, 2009
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 **G-CSF** biosimilar products (2012)
- Guideline on non-clinical and clinical evaluation of **monoclonal antibody** biosimilar products (in preparation 2013)
● Principle of Biosimilar Approach
Reference Product

- The approval of the biosimilar product should be based on the demonstration of similarity to a chosen reference product
  - Reference product should be already approved on the basis of a complete dossier package in Korea
  - Use of non-Korean (out-sourced) reference product may be acceptable, but provided that sufficient information about the comparability to Korean reference product in quality
Quality

- The comprehensive characterization and comparison at quality level are most important
  - Full CMC and comparability test data between biosimilar product and reference product are required
  - Using the sufficient number of reference product lots is important to justify acceptance criteria of each comparability test
    - Including “old” and “fresh” lot of reference product
Comparability

- All head-to-head comparability test results should satisfy acceptance criteria
- Rationale of acceptance criteria are required too
- Any difference between reference and biosimilar product should be assessed the impact of that, especially related with safety and/or efficacy
Justification of **Acceptance Criteria**

- Most important thing in development of biosimilar
- But most difficult task to developer of biosimilar
  - Should achieve comprehensive understanding about reference product
  - Should set their production within the criteria and stabilize simultaneously
- and also same thing happen to “Reviewer”
- Why difficult?
  - Development of new and precision analytical methods
    - "How similar is similar?"
  - Variety of test method
  - Improvement in production method and/or control
    - Enable to remove undesired microheterogeneity of reference
  - Process change and lot variation of reference product
  - In some cases, lack of understanding about relationship with clinical outcome, including safety
Non-clinical Study

- 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 based bioassay.....
  - *In vivo* study
    - Biological/Pharmacodynamic studies relevant to the clinical application
Toxicity

- At least one comparative repeat dose toxicity study are required
- Including toxicokinetic study and anti-drug antibody measurement

Condition for omission of animal study

- Enough evidence for comparability in quality & *in vitro* test
- Relevant animal species are not exist
- Known toxicity which can observed in animal are not exist
Clinical Study

- Comparative clinical trials are required
  - Pharmacokinetic / Pharmacodynamic study
  - Clinical Efficacy & Safety equivalence trial
    - Equivalence margins should be pre-specified and justified

- Stepwise approach is recommended
  - Generally, PK similarity data is required before efficacy trial
- Pharmacokinetic (PK) Study
  - Considering Factors
    - PK characterization of reference drug
    - Clinical usage
    - Safety ......
  - Preferred a single dose study in healthy volunteer
    - Not possible for any reason, study in patients is acceptable
    - If it is performed in healthy volunteer, PK study in patients is recommended during efficacy trial
● Efficacy trial

○ Randomized, parallel, comparative, double-blind and equivalent trial
  • Independent board for efficacy and/or safety data evaluation is recommended

○ Demonstration of comparability in efficacy and safety is main goal
  • Choose sensitive clinical model considered study condition and justified chosen indication
“Sensitive clinical model”

- **Scientifically**
  - Can detect possible difference between reference and biosimilar product
  - Can represent other indications to be extrapolated

- **Clinically**
  - Can use sufficient efficacy and safety data about reference product
  - Can reflect clinical usage in Korea
Immunogenicity

- Immunogenicity test are recommended to perform in the all non-clinical and clinical study
- Excluding exceptional case, independent clinical study to compare immunogenicity are not required
- Although tendency of immunogenic profile should be compared, but similarity are not excluded in case that biosimilar product is less immunogenic than reference product
  - In this case, some consideration may be required about efficacy
Extrapolation of Indications

- Sufficient safety and efficacy information should be provided for each indications of the reference product.
  - In this regards, reference products’ indication of which re-examination (PMS) are under monitoring cannot be extrapolated.
    - Remsima, biosimilar of infliximab, cannot be extrapolated “juvenile Crohn’s disease” which are not terminated PMS in Korea.
Conditions of extrapolation

- Sensitive clinical model to detect potential differences are used
- Clinically relevant mechanism of action and involved receptor are same in different indication
- Safety and immunogenicity have been sufficiently characterized
Post Marketing Surveillance

- In Korea, most biopharmaceuticals should be performed PMS, “re-examination”
  - Re-examination is active pharmacovigilance program including efficacy evaluation
  - New drugs are required 6 years PMS
    - Some case of adding indication are imposed 4-year PMS to added indication separately
  - 4 years PMS is required about follow on products (not originator)
PMS of biosimilar product

- PMS study plan should be submitted and discussed with MFDA before marketing of a biosimilar product
- The PMS plan should be contained sufficient number of patients for each extrapolated indication
- The results of PMS study should be reported to and discussed with MFDS periodically
Issues and Challenges

- Determination of bio-similarity
  - Justification of acceptance criteria

- Parallel conduct of PK/PD study and confirmative study

- Extrapolation of indication
  - Rationale of extrapolation
    - Cancer and Autoimmune disease
    - Various cancers
Status of Biosimilar development in Korea
Status of Biosimilar development

- MFDS recommended to stakeholder to discuss with us in early stage of biosimilar development and began consultation since 2009

- MFDS–Industry Joint Meeting Program for biosimilar development (2011~2012)
  - 11 biosimilar manufacturers
  - 24 Pre-IND sponsor meetings about 21 biosimilar products
• **IND**
  ◦ 9 local companies and 1 multi-national company has been approved biosimilar IND in Korea
  ◦ 12 local trials and 8 global trials including Korea about 7 reference products
  ◦ 16 phase 1 trials and 4 phase 3 trials

• **BLA**
  ◦ Approved : 1 local developed biosimilar product (Ramsima)
  ◦ Reviewing : 2 local and 1 imported biosimilar products
Summary

- In Korea, biosimilar products are developed actively
- Biosimilar regulation poses a number of substantial scientific and regulatory challenges for us
  - Acceptance criteria, extrapolation, PMS ……
- In spite of short experience about reviewing biosimilar, high degree of similarity in quality between biosimilar and reference product is a crucial key in the approval process
Thank you!
감사합니다!

Fax : 82-43-719-3500
E-mail : bkmwhite@korea.kr