Korean Perspective: Recent Trends in the Regulation of Biopharmaceuticals

Dec. 3, 2018

Gi Hyun Kim

Ministry of Food and Drug Safety, Korea
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Introduction of MFDS
Ministry of Food and Drug Safety

- **Function** *(Government Organization Act (Article 25))*

  “In order to administer duties concerning the safety of foods and drugs, Ministry of Food and Drug Safety shall be established under the Prime Minister.”

- **Staff** *(Total 1,858 government officers, Jul. 2018)*
  - Headquarters : 598 officers
  - NIFDS : 423 officers
  - Regional FDA : 837 officers
History of MFDS

1996 - Food and Drug Safety Headquarters (in April)

1998 - Korea Food and Drug Administration (KFDA)
  2 divisions, 6 departments and 5 chief officers,
  8 departments, 23 sections (776 officers)

2005 - Restructured to 6 bureaus and 4 departments
  1 office, 5 bureaus and 48 divisions (1,413 officers)

2009 - Reorganized in 2009
  1 office, 5 bureaus and 48 divisions (1,413 officers)

2010 - Relocation to Osong Health Technology Administration Complex, Osong, Chungbuk

2013 - Restructured to Ministry of Food and Drug Safety
  (1,449 → 1,760 officers)
MFDS Headquarters

Minister

Vice Minister

Spokesperson

General Affairs Division

- Audit and Inspection Office
- Criminal Investigation Office

Directors General for Planning and Coordination

- Planning and Finance Office
- Organization and Management Innovation Office
- Regulatory Reform and Legal Affairs Office
- International Cooperation Office
- ICT Management and Statistics Office
- Customer Support Office
- Emergency Planning and Safety Office

Customer Risk Prevention Bureau

- Customer Risk Prevention Policy Division
- Communication and Cooperation Division
- Risk Information Division
- Integrated Food Information Service Division
- Laboratory Audit and Policy Division

Food Safety Policy Bureau

- Food Safety Policy Division
- Food Safety Management Division
- Food Safety Labeling and Certification Division
- Health Functional Food Policy Division
- Alcoholic Beverages Safety Management and Planning Division
- Food Standard Division
- Residues and Contaminants Standard Division
- Food Additives Standard Division

Food and Consumer Safety Bureau

- Dietary and Nutritional Safety Policy Division
- Agro-Livestock and Fishery Products Policy Division
- Agro-Fishery Products Safety Division
- Foodborne Diseases Prevention and Surveillance Division

Pharmaceutical Safety Bureau

- Pharmaceutical Policy Division
- Pharmaceutical Management Division
- Narcotics Policy Division
- Narcotics Management Division
- Pharmaceutical Quality Division
- Clinical Trials Management Division
- Pharmaceutical Approval and Patent Management Division
- Pharmaceutical Safety Evaluation Division

Biopharmaceuticals and Herbal Medicine Bureau

- Biopharmaceutical Policy Division
- Biopharmaceutical Quality Management Division
- Herbal Medicine Policy Division
- Cosmetics Policy Division
- Quasi-Drug Policy Division

Medical Device Safety Bureau

- Medical Device Policy Division
- Medical Device Management Division
- Medical Device Safety Evaluation Division

Imported Food Safety Policy Bureau

- Imported Food Policy Division
- On-site Inspection Division
- Imported Food Inspection Management Division
- Imported Food Distribution Safety Division
NIFDS (Affiliated agency)

Director General

- General Affairs Division
- Research Planning & Management Division
- Vaccines Division
- Blood Products Division

Food Safety Evaluation Department
- Food Safety Risk Assessment Division
- Pesticide and Veterinary Drug Residues Division
- Food Contaminants Division
- Food Microbiology Division
- Food Additives and Packages Division
- Nutrition and Functional Food Research Team
- New Hazardous Substances Team
- Novel Food Division

Drug Evaluation Department
- Drug Review Management Division
- Pharmaceutical Standardization Division
- Cardiovascular and Neurology Products Division
- Oncology and Antimicrobial Products Division
- Gastroenterology and Metabolism Products Division
- Bioequivalence Evaluation Division

Biopharmaceuticals and Herbal Medicine Evaluation Department
- Biologics Review Management Division
- Biologics Division
- Recombinant Products Division
- Cell and Gene Therapy Products Division
- Herbal Medicines Division
- Cosmetics Evaluation Division

Medical Device Evaluation Department
- High-tech Medical Devices Division
- Cardiovascular Devices Division
- Orthopedic and Restorative Devices Division
- Dental and Gastroenterology Devices Division
- In-vitro Diagnostic Device Division

Pharmaceutical and Medical Device Research Department
- Drug Research Division
- Biologics Research Division
- Advanced Therapy Products Research Division
- Herbal Medicine Research Division
- Cosmetics Research Team
- Medical Device Research Division

Toxicological Evaluation and Research Department
- Toxicological Research Division
- Toxicological Screening and Testing Division
- Pharmacological Research Division
- Clinical Research Division
- Advanced Analysis Team
- Laboratory Animal Resources Division
Biopharmaceuticals Review Management Division

After (2016~)

Applicant

Biopharmaceuticals Review Management

Biologics Division
Recombinant Protein Products Division
Cell and Gene Therapy Products Division
Biopharmaceutical Quality Management Division
Regional 6 FDS

Efficacy and Safety Review
GMP inspection
Biopharmaceuticals in Korea
A biopharmaceutical is a preparation derived from living organisms or their products and it requires a special care for the sake of public health. This includes vaccines, plasma derivatives, antitoxin, recombinant DNA products, cell culture derived products, cell therapy products, gene therapy products and other products and agents with similar properties.

(MFDS notification)
Overview of Pharmaceutical Safety Management System

- GLP: Non-clinical
- GCP: Clinical
- GMP: Manufacture (Import)
- GSP: Distribution

Approval/Review
- Safety & Efficacy
- Quality

Manufacture (Import)
- Manufacture
- Import

Distribution
- Hospital
- Pharmacy
- Wholesaler

Usage after approval
- Consumer
- Doctor
- Pharmacist

- Post-approval Change
- Discontinue Manufacture/Import
- Recall/Discard
- Provide Information

- Research Development
- Patients (Confirm Safety and Efficacy)
- Set Manufacture/Quality Standards

Clinical Trials, Approvals

Manufacture (Import) Distribution

Post-marketing Management

Safety Management
Re-evaluation
Re-examination + Risk Management Plan

Issue, Safety Info.

Quality Inspection

Set Manufacture/Quality Standards

Ministry of Food and Drug Safety
Development History of Biological Products

- **Smallpox vaccine** (1800)
- **Antitoxin** (1890)
- **Polio vaccine** (1950)
- **First, FDA-approved blood coagulation factor VIII** (1966)
- **First, FDA-approved protein recombinant product: insulin** (1982)
- **First, FDA-approved antibody drug: OKT3** (1986)
- **First, FDA-approved biochip: AmpliChip CYP450** (2004)
- **First, anticancer immune cell therapy product: Provenge** (2010)
- **First, EMA-approved gene therapy product: Glybera** (2015)
- **WHO PQ vaccine: Euvax B** (1996)
- **Anticancer immune therapy: Immuncel-LC** (2007)
- **The world's first approval of stem cell product: Hearticellgram** (2011)
- **First cellular gene therapy product: Invossa** (2017)
- **First cell therapy product: Chondron** (2001)
- **The world's first approval of biosimilar mAb therapy: Remsima** (2012)
- **Herzuma** (2013)

Drug Safety
Updates on Biosimilars in Korea
### Current Status of Biosimilar Products in Korea

8 Biosimilar products developed in Korea

<table>
<thead>
<tr>
<th>No</th>
<th>Company</th>
<th>Drug name</th>
<th>Active ingredient</th>
<th>Indication</th>
<th>Approval date</th>
<th>EMA Approval</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Celltrion</td>
<td>Remsima 100mg</td>
<td>Infliximab</td>
<td>Rheumatoid Arthritis</td>
<td>Jul 20, 2012</td>
<td>Remsima (Sep 10, 2013)</td>
<td>Inflectra (Apr 5, 2016)</td>
</tr>
<tr>
<td>2</td>
<td>Celltrion</td>
<td>Herzuma 150, 440mg</td>
<td>Trastuzumab</td>
<td>Breast Cancer</td>
<td>Jan 15, 2014</td>
<td>Herzuma (Feb 9, 2018)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Samsung Bioepis</td>
<td>Etoloce 50mg</td>
<td>Etanercept</td>
<td>Rheumatoid Arthritis, Psoriasis</td>
<td>Sep 7, 2015</td>
<td>Benepali (Jan 14, 2016)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Samsung Bioepis</td>
<td>Remaloc 100mg</td>
<td>Infliximab</td>
<td>Rheumatoid Arthritis</td>
<td>Dec 4, 2015</td>
<td>Flixabi (May 26, 2016)</td>
<td>Reneflexis (Apr 21, 2017)</td>
</tr>
</tbody>
</table>
# Current Status of Biosimilar Products in Korea

- 16 Biosimilar approved in Korea (2018, 11)
  - 8 domestic products, 8 global products

- 8 Biosimilar products developed in Korea

<table>
<thead>
<tr>
<th>No</th>
<th>Company</th>
<th>Drug name</th>
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<th>Indication</th>
<th>Approval date</th>
<th>EMA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Samsung Bioepis</td>
<td>Samfenet 150mg</td>
<td>Trastzumab</td>
<td>Breast Cancer, Gastric cancer</td>
<td>Nov 8, 2017</td>
<td>Ontruzant (Nov 15, 2017)</td>
</tr>
<tr>
<td>7</td>
<td>Samsung Bioepis</td>
<td>Hadlima 40mg</td>
<td>Adalimumab</td>
<td>RA, Psoriatic Arthritis</td>
<td>Sep 20, 2017</td>
<td>Imraldi (Aug 24, 2017)</td>
</tr>
<tr>
<td>8</td>
<td>LG Chem Ltd.</td>
<td>Euepct Prefilled Syringe</td>
<td>Etarnercept</td>
<td>RA, Psoriatic Arthritis, etc</td>
<td>Mar 16, 2018</td>
<td></td>
</tr>
</tbody>
</table>
1. What is a Biosimilar product?

Biological products are usually recombinant protein molecules manufactured in living organisms by biotechnology. Most biologic products are difficult to identify or characterize due to the inherent variability based on highly complex manufacturing processes and structural complexity. As with small molecules drugs, the expiration of patents provides an opportunity for generic version of biological products to enter the market. Since biological product can not be an identical copy of the originator products, the term ‘biosimilars’ is used instead of ‘biogenic’.

Biosimilar products are defined as a biological product that is comparable to already marketed reference products in terms of quality, safety and efficacy. It would therefore be mandatory to demonstrate their comparability to a reference product through an extensive comparability exercise of the quality, non-clinical and clinical studies.

(Guidelines on Evaluation of Biosimilar Products, MFDS Guideline 2015)
(Regulation on Approval and Review of Biological Products, MFDS Notification)

2. How to develop the biosimilar product?

Manufacturers can develop a biosimilar product based on knowledge of safety and efficacy from clinical experience of a reference product. It is critical to demonstrate biosimilarity to the reference product using comprehensive head-to-head comparison in physicochemical & biological characteristics, and immunogenicity, efficacy and safety, through quality, non-clinical, clinical studies by a stepwise-approach.
Biosimilar

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IPRP Biosimilars Working Group

Members

- **Chair**: Dae Chul Kim, MFDS, KOREA
- **Co-Chair**: Stephanie Hardy, Health Canada, CANADA
- **Number of experts**: 35
- **Parties** involved in the Working Group
  - **11 Countries**: Brazil, Canada, Chinese Taipei, EU, Japan, Korea, Mexico, Saudi Arabia, Singapore, Switzerland, USA
  - **3 Organizations**: WHO, PANDRH, EAC
Reflection Paper on Extrapolation of Indications

◆ Objective

- Publication of scientific ‘reflection paper on extrapolation of indications in authorization of biosimilar products’

◆ Contents

- General Considerations
  1. Principles for Demonstrating Biosimilarity
  2. Principles for Extrapolation of Indications

- Specific Considerations for the Extrapolation of Indications
  1. Evidence from Analytical Comparability Study
  2. Evidence from *in vitro* and/or *in vivo* Functional Studies
  3. Evidence from Clinical Studies
  4. Evidence from Publicly Available Information
  5. Evidence to be Provided where a Residual Uncertainty Remains
Reflection Paper on Extrapolation of Indications

◆ Attachment

1. Gap analysis of biosimilar guidelines for the extrapolation of indications
2. Biosimilar products approved with extrapolated indications
3A. Selected summary of regulatory biosimilar reviews by year
3B. Selected summary of regulatory biosimilar reviews by agent
Reflection Paper on Extrapolation of Indications

Factors for the justification of the extrapolation of indication:
* most sensitive for detecting differences
* relevant mechanism(s) of action
* mechanism(s) of the disease (or conditions)
* any factor (affecting safety profile including immunogenicity)
Recent Changes for Safety and Regulatory Reforms
1. Accelerated Review for Biopharmaceuticals

- **Objective:** Reinforcement of patient’s accessibility to medicine for the treatment of life-threatening disease, etc.

- **Regulation:**
  Regulation on Biopharmaceuticals Approval and Review (Revised and implemented in Jul, 2016)

- **Main Contents**
  - Expand to accelerated review: Life threatening disease, No available therapies, Bioterrorism, Pandemic vaccines → Significantly advanced in safety and efficacy in a severe disease
  - Designation of accelerated review for biopharmaceuticals

- Establishment of the procedure of Designation of accelerated review for biopharmaceuticals (Nov. 2017)
2. Expand Risk Management Plan

- **Objective:** Comprehensive risk management across lifecycle to improve the safe use of medicinal products
- **Regulation:** Regulation on Pharmaceuticals Approval, Notification & Review
  Regulation on Safety of Medicinal Products, etc.
  *(Both, Implemented in Jul. 2015)*

**Phase 1 (Jul. 1, 2015)**
- New drugs
- Orphan drugs
- Products designated by the Minister
- Products applied by manufacturers

**Phase 2 (Jul. 1, 2016)**
- All NDA Drugs with different APIs or composition ratio (compared with previously approved pharmaceuticals)

**Phase 3 (Jul. 1, 2017)**
- All NDA Drugs with different route of administration (compared with previously approved pharmaceuticals)

**Phase 4 (Jul. 1, 2018)**
- All NDA Drugs added new indications (in addition to previously approved indications)
3. Strengthen Life Cycle Safety Management in Biopharmaceuticals

- **Objective:** Ensure safe use of biopharmaceuticals and ethical foundation for cell donation

- **Regulation:**
  Regulation on Biopharmaceuticals Approval and Review
  (*Notification No. 2017-72, Revised and implemented in Aug., 2017*)

- **Main Contents**
  - **Label biopharmaceuticals for scientific information** (e.g. pharmacology, clinical pharmacology, and clinical data)
    → Provide health professionals for safe use
  - **Informed consent on cell therapy and gene therapy product**
    : intended use(s) of donated cells, donor screening tests, donor’s rights and privacy protection including withdrawal of the consent
4. Revised Definition of Gene Therapy

- **Objective:** Reflection of new advanced biotechnology-derived products in regulation

- **Regulation:**
  Regulation on Biopharmaceuticals Approval and Review
  *(Revised and implemented in Jun, 2017)*

- **Main Contents**
  A medicinal product which contains either
  - Genetic material to influence the gene expression, or
  - Genetically modified, or genetic material-transduced cells
5. Association for advanced biopharmaceuticals

- **Objective:** Support and guide for the **convergence product using advanced biotechnology** (artificial skin, artificial cornea, heterogeneous organ, etc.)

- **Organization:** **Association of Innovative Product Technical Support**

- **Activity**
  - Classify the products and support for their development

  - Classified 3D bioprinted products as drug-device combination products / drugs (cell therapies)
6. Investigator clinical trial under HRPP

- **Regulation**: 
  Regulation on approval of clinical trials (revised on June 2018)

- **Article**: exemption of clinical trial approval:
  investigator clinical trial with the IRB approval of the institute under HRPP (human research protect program)

- **Clause**
  - Confirm drug interaction or combined therapy within approval label information
  - Confirm bioavailability or bioequivalence of approval usage into health adult
7. Guideline on medicine using accompanying medicinal devices (2018. 06)

- **Objective**; approval drug and companion diagnostics for prediction of patient-specific reactivity by using biomarker as indicators

- **Contents**
  - explain how indication, usage and the precaution to use should be written, if the drug should be used and was developed with specific diagnostics
  - Consideration for clinical trials and approval process

- **Objective**: genetically modified cell with gene editing or genetic material expression or containing gene editing material

- **Contents (general information)**
  - Describe gene editing material; gRNA, nuclease / plasmid or virus vector / delivery method
  - Rationale for target gene / editing method / expression pattern
  - Target gene mutation (allele, SNP, mutation)

- **Objective**: therapeutics with extracellular vesicle secreted by cells or genetically modified cells

- **Contents (general information)**
  - **Definition**: extracellular vesicle with lipid bilayer secreted by cell. Not including cell substrate and cell lysate and cell mimetics with cell fragments
  - **Characterization**: RNA content, protein profile, lipid content, amount and size of extracellular vesicle
Thank you for your attention

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