Korean Perspective : Recent Trends in the Regulation of Biopharmaceuticals

Dec. 4, 2017
Heajeong Doh

Ministry of Food and Drug Safety, Korea
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• Introduction of MFDS
• Biopharmaceuticals in Korea
• Recent Changes for Safety and Regulatory Reforms
• Updates of Biosimilar in Korea
Introduction of MFDS
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 1,797 government officers, 2017.9.)

- **Headquarter**: 589 officers
- **NIFDS**: 418 officers
- **Regional FDA**: 790 officers

Budget (year 2017)

About 40 billion USD
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**: Reorganized in 2009
  - 1 office, 5 bureaus and 48 divisions (1,413 officers)
- **2009**: Restructured to 6 bureaus and 4 departments
  - (1,200 regular employees)
- **2010**: Relocation to Osong Health Technology Administration Complex, Osong, Chungbuk
- **2013**: Restructured to Ministry of Food and Drug Safety
  - (1,449 → 1,760 officers)
Before

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 Review Management Division

After

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
- Usage after approval

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

2. Approval/Review
   - Safety & Efficacy
   - Quality

3. Manufacture (Import)
   - Manufacture
   - Import

4. Distribution
   - Hospital
   - Pharmacy
   - Wholesaler

5. Usage after approval
   - Consumer
   - Doctor
   - Pharmacist

6. Post-approval Change
   - Discontinue Manufacture/Import
   - Recall/Discard
   - Provide Information (Safety Letters)

7. Quality Inspection

8. Clinical Trials, Approvals

9. Post-marketing Management
Annual Drug Approval & Notification

Approval (2010~2016)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Approval</th>
<th>Notification</th>
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<tbody>
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<td>614</td>
<td>916</td>
</tr>
<tr>
<td>'11</td>
<td>853</td>
<td>337</td>
<td>516</td>
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<td>'12</td>
<td>831</td>
<td>375</td>
<td>456</td>
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<tr>
<td>'13</td>
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<td>1,088</td>
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<tr>
<td>'14</td>
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<td>1,644</td>
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<td>'15</td>
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<td>'16</td>
<td>2,030</td>
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Ministry of Food and Drug Safety
## Annual New Drug Approval

<table>
<thead>
<tr>
<th>New Drug</th>
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<tr>
<td></td>
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<table>
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<tr>
<td>No of items (No of Active ingredients)</td>
<td>49 (26)</td>
<td>31 (22)</td>
<td>17 (14)</td>
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<td>New Drugs Developed in Korea</td>
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<td>2</td>
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<td>1</td>
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<td>6</td>
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<td>Biopharmaceuticals</td>
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<tr>
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< New Drugs Developed in Korea >

### Annual IND Approval

**last 3 years Approval for IND**

<table>
<thead>
<tr>
<th>Year</th>
<th>Sponsor trials</th>
<th></th>
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<tr>
<td></td>
<td>Domestic</td>
<td>Multi-national</td>
<td>Total</td>
<td>Sponsor-Investigator trials</td>
<td>Total</td>
</tr>
<tr>
<td>2014</td>
<td>220</td>
<td>285</td>
<td>505</td>
<td>148</td>
<td>653</td>
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<tr>
<td>2015</td>
<td>245</td>
<td>295</td>
<td>540</td>
<td>134</td>
<td>674</td>
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<tr>
<td>2016</td>
<td>190</td>
<td>267</td>
<td>457</td>
<td>171</td>
<td>628</td>
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</tbody>
</table>

- Decrease the approval for IND
- Increase the Sponsor-investigator trials
## Annual IND Approval

- **Approval for IND by clinical trial phase**

<table>
<thead>
<tr>
<th>year</th>
<th>Domestic</th>
<th></th>
<th></th>
<th>Multi-national</th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Phase 1</td>
<td>Phase 2</td>
<td>Phase 3</td>
<td>Other</td>
<td>Total</td>
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<td>42</td>
<td>1</td>
<td>220</td>
<td>40</td>
<td>51</td>
<td>190</td>
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<tr>
<td>2015</td>
<td>148</td>
<td>42</td>
<td>53</td>
<td>2</td>
<td>245</td>
<td>50</td>
<td>73</td>
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<tr>
<td>2016</td>
<td>123</td>
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<td>39</td>
<td>3</td>
<td>190</td>
<td>57</td>
<td>71</td>
<td>136</td>
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</table>
### Annual IND Approval

#### Approval for IND by drug type

<table>
<thead>
<tr>
<th>year</th>
<th>Chemicals</th>
<th>Biologics</th>
<th>Recombinant</th>
<th>Cell therapy</th>
<th>Gene therapy</th>
<th>Total</th>
<th>Herbal medicine</th>
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<tr>
<td>2014</td>
<td>465 (71%)</td>
<td>29</td>
<td>110</td>
<td>24</td>
<td>7</td>
<td>170</td>
<td>18 (3%)</td>
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<tr>
<td>2015</td>
<td>451 (67%)</td>
<td>14</td>
<td>158</td>
<td>25</td>
<td>5</td>
<td>202</td>
<td>21 (3%)</td>
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<tr>
<td>2016</td>
<td>387 (62%)</td>
<td>33</td>
<td>151</td>
<td>33</td>
<td>9</td>
<td>226</td>
<td>15 (2%)</td>
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</tbody>
</table>
Annual IND Approval

- Approval for IND by drug classification

<table>
<thead>
<tr>
<th>Year</th>
<th>Cancer</th>
<th>Cardiovascular</th>
<th>Hormones</th>
<th>Central Nervous System</th>
<th>Digestive</th>
<th>Urinary</th>
<th>Antibiotics</th>
<th>Respiratory</th>
<th>Immune Suppressors</th>
<th>Blood</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>210</td>
<td>90</td>
<td>55</td>
<td>58</td>
<td>33</td>
<td>32</td>
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<td>2015</td>
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<td>43</td>
<td>25</td>
<td>23</td>
<td>16</td>
<td>80</td>
<td>674</td>
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<tr>
<td>2016</td>
<td>202</td>
<td>50</td>
<td>39</td>
<td>51</td>
<td>48</td>
<td>16</td>
<td>55</td>
<td>20</td>
<td>32</td>
<td>20</td>
<td>95</td>
<td>628</td>
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</tbody>
</table>
## Approval for IND of Anticancer drug

<table>
<thead>
<tr>
<th>year</th>
<th>Target</th>
<th>Immune</th>
<th>other</th>
<th>total</th>
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</thead>
<tbody>
<tr>
<td>2014</td>
<td>123</td>
<td>29</td>
<td>58</td>
<td>210</td>
</tr>
<tr>
<td>2015</td>
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<tr>
<td>2016</td>
<td>86</td>
<td>68</td>
<td>48</td>
<td>202</td>
</tr>
</tbody>
</table>
Recent Changes for Safety and Regulatory Reforms
• 1st : Expand the therapeutic opportunities for patient-centered drug use

• 2nd : Ensure safety of the patients

• 3rd : Prepare the 4th industrial revolution era
1. Strategies for Stable Supply of National Essential Drugs

- **Objective:** Stable supply of National Essential Drugs (NEDs)  
  Announced ‘Strategy for Stable Supply of NEDs’ (Oct. 2016)

- **Regulation:**  
  - Pharmaceutical Affairs Act  
    *(Revised in Dec. 2016, To be implemented in Dec. 2017)*

- **Main Contents**  
  - Develop & Operate ‘National Management System’  
  - Designate NED list / Make annual plan for supply of NEDs  
  - Establish supply plans against shortage of NEDs  
  - Establish risk management against threats to public health
2. 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 the accelerated review: Life threatening disease, No available therapy exist, Bioterrorism, pandemic vaccines → **Significantly advanced in safety and efficacy in severe disease**
  - Designation of accelerated review for biopharmaceuticals

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

- **Objective:** Comprehensive risk management across lifecycle to improve the safe use of medicinal product

- **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)
4. 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
5. Label all ingredients on container & packaging

❖ Objective:
Promote the public’s **right to know & right to health**

❖ Regulation:
• Pharmaceutical Affairs Act *(Revision)*
  *(Revised in Dec., 2016, To be implemented in Dec., 2017)*
• Regulation on Safety of Medicinal Products, etc.
  *(Legislation Notice in Dec., 2016)*

❖ Main Contents
• **All ingredients should be labeled** on container or packaging
6. Registration Renewal System

- **Objective**: To extend the valid marketing authorization of pharmaceuticals with submission of required data (every 5 years)

- **Regulation**:
  - Pharmaceutical Affairs Act (*Revision, Implemented in Jan., 2013*)
  - Regulation on registration renewal system (*Implemented in Sep., 2016*)

<table>
<thead>
<tr>
<th></th>
<th>Drugs</th>
<th>Orphan drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>After Jan. 1, 2013</strong></td>
<td>Renew every 5 years, except for APIs, export drugs</td>
<td>Renew every 10 years</td>
</tr>
<tr>
<td></td>
<td><em>Expired in January 2018</em></td>
<td><em>Orphan Drug Act: Implemented Dec. 28, 2016</em></td>
</tr>
</tbody>
</table>

*Pharmaceutical products approved before January 2013 are renewed by designated expiration date based on pharmaceutical indication codes.*
7. Revised the 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
- Genetically modified, or genetic material-transduced cells
8. 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 product and support to develop

  - Classified the 3D-Bioprinting as a drug-device combination product / drug(cell therapy)
Objective: For the collaboration in the Prequalified vaccines, MFDS & WHO agreed on ‘Collaboration Arrangement’ (Dec. 2016)

Main Contents

• Exchange regulatory information on PQ vaccines
  - GMP inspection certificate and report
  - national releases of the vaccine lots
  - notifications of serious/unexpected adverse events

• Keep confidentiality on the exchanged information

* 17 Prequalified Vaccines (4 Korean manufacturers)

(In total, 240 Vaccines in 22 countries as of 12 May 2017)
10. Revised the guideline for the evaluation of post-approval manufacturing changes

**Objective:** Clarification the types of post-approval changes and the data requirement *(will be revised in Dec. 2017)*

<table>
<thead>
<tr>
<th>2009</th>
<th>2017 (will be revised)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Guideline for evaluation of post-approval manufacturing changes</td>
<td>• Guideline for evaluation of post-approval manufacturing changes</td>
</tr>
</tbody>
</table>

Annex 1
- Vaccine of data requirement for quality changes

Annex 2
- Recombinant product of data requirement for quality changes

**Main Contents**

- The types of post-approval manufacturing changes: to classify *frequently occurring changes* as major, moderate, minor etc.
- **Data requirements** for the each cases in detail of **Vaccines and Recombinant product**
Updated of Biosimilar in Korea
## Current Status of Biosimilar products in Korea

- **22 Biosimilar candidates (as of 2017)**
  - 12 domestic products, 10 global products

- **5 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>
</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>
</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>
</tr>
<tr>
<td>3</td>
<td>Samsung Bioepis</td>
<td>Brenzys 50mg</td>
<td>Etarnercept</td>
<td>Rheumatoid Arthritis, Psoriasis</td>
<td>Sep 7, 2015</td>
</tr>
<tr>
<td>4</td>
<td>Samsung Bioepis</td>
<td>Renflexis 100mg</td>
<td>Infliximab</td>
<td>Rheumatoid Arthritis</td>
<td>Dec 4, 2015</td>
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<tr>
<td>5</td>
<td>Celltrion</td>
<td>Truxima</td>
<td>Rituximab</td>
<td>Rheumatoid Arthritis, Lymphoma</td>
<td>Jul 16, 2015</td>
</tr>
</tbody>
</table>
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 (affect safety profile including immunogenicity)
Biosimilar

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 ‘biogeneric’.

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.
Thank you for your attention

Heajeong Doh
hjdo@korea.kr