Korean Perspective: Recent Trends in the Regulation of Biopharmaceuticals

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Introduction
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 1,774 government officers, 2016.10.

- Headquarter: 584 officers
- NIFDS: 408 officers
- Regional FDA: 782 officers

**Budget**

Year 2016

- About 390 million USD
MFDS Vision, Mission, and Policy Strategy

Safe Food and Drug, Healthy Nation, Well-being Society

VISION

MISSION

POLICY STRATEGY

- Ensuring safety of the people to improve quality of life
- People-oriented safety management from farm to table
- Realization of safer and healthier lives of the people
- Beyond safety, providing assurance to the people

- We will do our best to keep off adulterated food from the public
- We are dedicated to providing better service for industries
- We will increase collaboration and communication with relevant agencies to expand safety net for the people’s happiness
- We will look ahead and prepare for the healthy centenarian era
Vision and Goals of biopharmaceutical policies

Vision

To Join the ranks of bio powers

Goals

1. Build a solid foundation for a safer use of biopharmaceuticals
2. Advance a quality assurance mechanism based on science and technologies
3. Improve the international standing of Korea’s biopharmaceutical industry
Biopharmaceuticals in Korea
A biopharmaceutical is a preparation derived from living organisms or their products and it requires special care for the sake of public health. This includes vaccine, plasma derivatives, antitoxin, recombinant DNA product, cell culture derived products, cell therapy products, gene therapy products and other products and agents with similar properties.

(MFDS notification)
Milestones of Biopharmaceuticals in Korea

1800
- Small pox vaccination (1800)

1900
- Anti-toxin (1890)
- Live polio vaccine (1950)
- 1°FDA approved Factor VIII (1966)
- 1°FDA approved recombinant DNA product: insulin (1982)
- 1°FDA approved therapeutic monoclonal antibody: OKT3 (1986)

2000
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- 1°FDA approved therapeutic monoclonal antibody: OKT3 (1986)

WHO Pre-qualified vaccine: EUVAX B(1996)*

MFDS approved 1st cell therapy product: Chondron (2001)

MFDS approved pandemic H1N1 influenza vaccine: Green Flu-S(2009)


MFDS approved 1st Mab biosimilar: Remsima (2012), Herzuma (2014)

So far, 8 vaccines have been pre-qualified by WHO.
Industry Trends (1)

Domestic medicines market grew an annual average of 2.4% in last 5 years

- Market size (100 mil KRW) in 2020 (MarketOptimizer, 2014)
- YOY growth rate (%)

Increased biopharmaceuticals market share of the entire pharmaceuticals market

- 8.4% in 2011 (1.6 trillion KRW) → 8.5% in 2015 (1.6 trillion KRW)
- Maintained a steady level of the last five years

Biopharmaceutical Products Approved (as of Aug., 2016)
- A total of 839 items approved (517 manufactured, 322 imported)
- Record (2015): 1.72 trillion KRW (produced), 84 million KRW (imported)

Biopharmaceutical exports, imports are on the increase
- Imports: 630 million USD in 2011 → 730 million USD in 2015 (up by 1.1 times)
- Exports: 260 million USD → 890 million USD in 2015 (up by 3 times)
Industry Trends (2)

Increased investments in biopharmaceuticals by large companies and pharmaceutical industry

- Samsung (investments of 2 trillion KRW), Celltrion (investments of 1.5 trillion KRW), Donga ST (80 billion KRW in a bio plant to be completed in May, 2014), etc.

Commercialization efforts in advanced biopharmaceuticals in last 3-4 years garnered successes

- World’s first stem cell therapy approved (Hearticellgram-AMI by Pharmicell, July, 2011)
- World’s first antibody biosimilar approved (Remsima by Celltrion, July, 2012)
- World’s third cell-cultured flu vaccine approved (Sky Cell Flu by SK Chemical, Dec., 2014)

Big jump in biopharmaceutical exports

- Biopharmaceutical exports in 2015 went up by 34% YOY : 790 million USD (Source : KoBia)
  ※ Production of a finished drug Quinvaxem (Jansen vaccines) ranked 1st (2008~2015)
- Remsima (biosimilar) ranked 1st in export amount in 2015 : 400.4 million USD
**Technology Trends**

Many domestically-developed biopharmaceuticals are expected to enter the market

- Technical gap compared to the country with the most advanced bio technologies: stem cell therapies (2.4 years), gene therapies (4.3 years)
  - Results of technical advancement level assessment in 2014 (Ministry of Future, Korea Institute of Science and Technology: May, 2014)
- Commercial clinical research of stem cell therapies: No. 2 in the world

<table>
<thead>
<tr>
<th></th>
<th>Development phase</th>
<th>Phase 1, 2 Clinical trials</th>
<th>Phase 3 Clinical trials</th>
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</thead>
<tbody>
<tr>
<td>Biosimilars</td>
<td>5</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Stem cell therapies</td>
<td>4</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Gene therapies</td>
<td>0</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Vaccines</td>
<td>9</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>18</strong></td>
<td><strong>38</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>

- Source: MFDS, October 2016

**Global stem cell therapy clinical trials**

- Israel 5%
- India 5%
- Germany 3%
- Malaysia 1%
- Panama 3%
- England 1%
- etc 3%

- Source: NIH, U.S., 2014

**Global gene therapy clinical trials**

- USA 62.7% [n=1368]
- UK 9.5% [n=209]
- Germany 3.8% [n=84]
- China 2.4% [n=54]
- France 2.4% [n=52]
- Switzerland 2.3% [n=50]
- Japan 1.9% [n=41]
- Netherlands 1.5% [n=34]
- Australia 1.4% [n=32]
- Canada 1.1% [n=30]
- Other countries 8.8% [n=155]

- Source: J Gene Med, 2015
## Biopharmaceutical Industry Status in Korea

<table>
<thead>
<tr>
<th></th>
<th>Vaccine</th>
<th>Plasma-derived product/Blood Component</th>
<th>Anti-Toxin/Toxin</th>
<th>Recombinant protein product</th>
<th>Cell therapy product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Manufacturer</td>
<td>11</td>
<td>20</td>
<td>4</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Importer (Global Company)</td>
<td>13</td>
<td>4</td>
<td>5</td>
<td>35</td>
<td>0</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing products</td>
<td>84</td>
<td>276</td>
<td>14</td>
<td>124</td>
<td>14</td>
</tr>
<tr>
<td>Imported products</td>
<td>66</td>
<td>34</td>
<td>6</td>
<td>215</td>
<td>0</td>
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(As of May. 2016)
Recent Changes in Safety and Regulatory Reforms
## Strengthened biopharmaceutical safety control (1)

### Expanded foundation for patient-centric use

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<tbody>
<tr>
<td>• Death Compensation (2015), disability compensation (2016), consultation fees (2017)</td>
<td>• New drug, orphan drug, stem cell therapy product, etc.</td>
<td>• Introduced post-approval investigation of all products approved (2015), and long-term follow-up (2017)</td>
</tr>
</tbody>
</table>

### Expand conditional approval of cell-therapy used to treat life-threatening illnesses (2016~)

- Conditional approval: grant approval with phase 2 clinical trials on condition phase 3 clinical trial data will be submitted at a later date

### Enhanced vaccine immunization records and adverse event evaluations

- Provision of stickers for baby journals to better check immunization records (2016)
- Vaccine adverse event linking systems (2015~2017)
  - MFDS – Korea Institute of Drug Safety & Risk Management – KCDC
Strengthened biopharmaceutical safety control (2)

- Advance pharmaceutical approval control mechanism
  
  Introduce a mechanism linking drug approval and drug pricing systems (2014)
  
  - Prior to new drug approval, approval results to be notified to Health Insurance Review & Assessment Service (HIRA), expediting insurance coverage evaluation processes to accelerate market introduction of new drugs
  
  Introduce a mechanism linking approval with patent (2015)
  
  - Help lower medical costs and increase R&D investments by expending late comer drugs
  
  Introduce of Generic drug CTD (July, 2016)
  
  - New drug (Mar, 2009), Biological Products (Mar, 2009)
  
  ‘Renewal of Drug Approval’ system (2018)
  
  - Effective for 5 years
  - Safety management data, quality management data, labeling, etc
Strengthened biopharmaceutical safety control (3)

- Establish quality assurance system based on scientific assessments

**Implement scientific national lot release mechanism**
- Differentiated control systems by making comprehensive risk evaluations (2016)

**Improve biopharmaceutical manufacturing and quality control**
- Newly put in place blood products manufacturing and quality control standards (GMP) (December 2016)
- Conduct GMP evaluations on orphan drugs, export products (July 2016)

**Develop Quality by Design (QbD) models, and guidance for QbD of recombinant DNA products (2016~2017)**
Enhance Biopharmaceuticals Industry’s competitiveness

- Support for biopharmaceutical commercialization

Reduce manufacturing burden by streamlining biopharmaceutical facility criteria

- (Before) Separate manufacturing facilities for vaccines and recombinants DNA products
  - (Improved) Communal manufacturing facilities (Dec., 31, 2015)
    - Manufacturing facilities can be shared for the recombinants DNA product, and vaccines manufactured with genetic engineering technologies
    - Provided that measures to prevent contamination are in place, and that there is no risk of cross-contamination

- Site inspection of manufacturing plants and consulting services to be provided even before the application for product approval has been made

- (Improved) Expand biopharmaceutical manufacturing plant inspections to be included in those subject to prior review
  - Following approval application, a maximum 70 days have been reduced compared to GMP evaluation

* For biopharmaceutical approval applications, guidelines for GMP evaluation and prior biopharmaceutical GMP review have been put in place (June 30, 2016).
Early settlement of advanced quality control systems

- Advance biopharmaceutical quality control mechanism

Put in place PIC/S-related “Regulations regarding drug manufacturing and quality control” (July 2015)

- Following the PIC/S joining, details have been determined to realize international harmonization regarding drug manufacturing and quality control criteria

Begin issuing drug GMP compliance certificate (October 2014)

- Following PIC/S joining, revise and implement “Regulation on Safety of Pharmaceuticals, etc.”
  - Drug manufacturers are allowed to market products after having the GMP compliance certificate issued

  - (New manufacturing plants) When evaluation is applied after the implementation date, evaluation (compliance) will be conducted before GMP compliance certificate is issued.

  - (Existing manufacturing plants) All dosage forms are re-evaluated for GMP compliance during the three year term regular drug surveillance, after which GMP compliance certificate is issued.
Provide regulatory and industry information to help advance overseas biopharmaceutical market

- Bio IT Platform (‘14~)
  - Overseas regulatory information, biologics approval regulations and guidelines, market information, consulting services (www.bpis.or.kr)

**Share**

- **Sharing of overseas regulatory information**
  - Provision of overseas biopharmaceutical regulatory information and guidelines (12 countries)
  - Sharing of market size, items, clinical trial approvals, and industry information (16 countries)

**Communication**

- Create communication channels between industry, academia, government
  - Create a forum where industry, academia, and government share project-related opinion
  - Run a global advancement subcommittee under Dynamic Bio
  - Head public opinions by conducting biopharmaceuticals industry and academia survey

**Cooperation**

- Establish cooperation network with relevant organizations
  - Link with overseas advancement support projects for pharmaceuticals
  - Create collaboration network with relevant organizations

**Opening**

- Better access to review/approval information
  - Provide biopharmaceutical review and approval results
  - Provide & promote biopharmaceutical policy information
    *Hold regulatory seminars; distribute leaflets about regulatory improvements*
Improve access for rare disease treatment options

Better the access for rare disease treatments using novel technologies

- With life-cycle support from clinical trials, approval and post-marketing phases, improve R&D and access for rare disease treatment options

- **Development**
  - When designated as an orphan drug, market size (production, import volume) requirements are not required

- **Approval**
  - Orphan drug manufacturing and GMP evaluation requirements to be relaxed
    - *GMP evaluation data:* (present) 3 manufacturing lots → (improved) 1 or more manufacturing lot data to be submitted
    - Prior review fees exempted for in-country developed orphan drugs (data regarding standards and test methods; and GMP data)

- **Marketing Distribution**
  - Extend validity for orphan drug approvals (5 years → 10 years)
  - Promote R&D with re-examination term for orphan drugs of less than 10 years
  - Support a stable public organization-led supply of orphan drugs
    - *Supply of orphan drugs by domestic drug manufacturers possible after the drugs are consigned-manufactured by Orphan Drug Center*
Updates on APEC RHSC Activity
Progress Toward Convergence
- History of the Biotherapeutics Roadmap

Born in 2011
[Biosimilar]

Phase 1: 2013~2014
[Biotherapeutics]
- rDNA, mAb, therapeutic Vaccines
- Workshop: gap analysis

Phase 2: 2015~2016
[Step for Convergence]
- Training /workshop
- E-learning, CoE, etc
- Regulation upgrade

APEC Biotherapeutic Products Roadmap
to reach a high level of regulatory convergence by 2020
# Specific activities and time frames

<table>
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<tr>
<th>Steps</th>
<th>Activities</th>
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<tbody>
<tr>
<td>Step 1: Assessment</td>
<td>• <strong>Assessment</strong> of regulatory environment and gaps between APEC members through gap analysis and workshop(‘13, ‘14)</td>
</tr>
</tbody>
</table>
| Step 2: Training/Workshop | • Develop training curriculum and conduct training and workshop(‘15)  
• Pilot CoE (‘16 ~ ‘17) : USA(Sep) & Korea(Nov)                                                                 |
| Step 3: Assessment of training | • Workshops to review the outcomes of Step 2 (‘18)  
• To review Post-implementation of international guidelines & other attempt                                                                 |
| Step 4: Training to reach the goal | • Recommendations to further highly regulatory convergence (‘19~’20) |
**2013**

The 1\textsuperscript{st} AHC Biotherapeutics Roadmap Workshop (September 25-27, Seoul, Korea)

**2014**

The 2\textsuperscript{nd} AHC Biotherapeutics Roadmap Workshop (May 12-13, Seoul, Korea)
Step 2

2015~2016

Working Group
- Assessment of step 1 and drawing of future strategies
- Design of training program
  - analyzing other training programs such as case studies from WHO as teaching tools
  - pilot training programs with written, audio, video and presentation formats

Training
- Small-topic-based training sessions/workshops
- Experts from NRAs, industries, academia will be the faculty
- CoE(Center of Excellence)
The 3rd AHC Biotherapeutics Roadmap Workshop (July 1-2, Incheon, Korea)
# Biotherapeutics CoE: Recommendations for 2016

| **WHO** (target audience) | • APEC member economies with demonstrated interest in harmonization  
| | • (vs. those with systems that are already harmonized or those in early stage of learning)  
| | • Regulators (CMC experts and clinical evaluators) |
| **WHAT** (curriculum) | 1) Comparability assessment of biotherapeutics throughout the product life cycle  
| | 2) Clinical considerations of biosimilars |
| **WHERE** (location) | • Numerous options (one CoE to cover both topics/network of collaborating CoEs)  
| | • Driven by availability of interested academic partners with relevant expertise  
| | • Seoul Natl Univ, Northeastern Univ, etc |
| **WHEN** (2016 pilot) | • Preferably, in first half of 2016 |
| **HOW** (Logistics) | • Online(e-learning) + Face-to-face  
| | • Theoretical + case studies + hands on  
| | • Certification or recognition of attendance to be granted |
Biotherapeutics CoE: Activity in 2016

- US Biotherapeutics CoE Pilot Workshop conducted at Northeastern University (Sep 13-16)

- Korea Biotherapeutics CoE Pilot Workshop conducted at Seoul National University (Nov 8-11)
2016 APEC Biotherapeutics CoE Pilot Korea Workshop

• **Title**: 2016 APEC Biotherapeutics CoE Pilot Korea Workshop

• **Date**: November 8-11, 2016

• **Venue**: Waters Korea & Glad Hotel, Seoul, Korea

• **Participation**: Regulatory Reviewers (14 participants, 13 countries)

• **Program**:

  Part 1: Introduction to Biologics - Online

  Part 2: Comparability throughout the Life-Cycle

  - *Hands-on training was held at Waters Korea*

  Part 3: Clinical Considerations for the Assessment for Biosimilars
Part 1: Introduction to Biologics

Part 2: Comparability throughout the Life-Cycle

Session 2: Control of the Product (Hands-on Training)
Session 3: Risk based understanding of categorization of changes (Lecture)
Session 4: Risk based understanding of categorization of changes (Hands-on Training)
Session 5: Biosimilar Development (Site Visit)

Part 3: Clinical Considerations for the Assessment for Biosimilars

Session 6: General Regulation in Biosimilar Development
Session 7: Clinical Elements of Biosimilar Development
Session 8: Case Studies and Discussion
Session 9: Extrapolation of Indication
Session 10: Post approval monitoring
Session 11: Wrap Up
Future Plan of APEC RHSC

• 2017 AHC Workshop (June, 2017)
  - Working area: Find additional area needed to be harmonized
  - CoE institute candidate

• APEC CoE
  - CoE Institute: NEU(USA), Korea CoE(TBD)
Updates of Biosimilar in Korea
Legislative basis of biosimilar products

- 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 were published
  - Erythropoietin(NC/C)(2011)
  - Somatropin(NC/C)(2011)
  - G-CSF(NC/C)(2012)
  - Monoclonal Antibody(NC/C)(2013)
  - Insulin/Insulin-analog(NC/C)(2015)
Definition of biosimilar products

- **Recombinant Protein Products (RPP)**: A medicinal product containing peptide or proteins produced by recombinant engineering as drug substance.

- **Biosimilar Products (SBP)**: A biological product that is proved to be comparable to already marketed reference products in terms of quality, safety and efficacy.
  * Regulation on Review and Authorization of Biological Products, MFDS

- **Reference Product (RBP)**: A biological product already approved by a regulatory authority on the basis of full registration dossier (licensed based on full quality, safety and efficacy data).
  * Guidelines on the Evaluation of Biosimilar Products, MFDS
Current Status of Biosimilar products in Korea

- **Popular reference products**
  - Adalimumab, Infliximab, Etanercept, Rituximab, Trastuzumab
Current Status of Biosimilar products in Korea

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

• 5 Korean biosimilar products authorized
  ✓ Remsima (Infliximab, July. 20, 2012)
  ✓ Herzuma (Trastuzumab, Jan. 15, 2013)
  ✓ Brenzys/Benepali (Etanercept, Sep. 7, 2015)
  ✓ Renfleksi/Flixabi (Infliximab, Dec. 4, 2015)
  ✓ Truxima (Rituximab, Nov. 17, 2016)
Thank you for your attention