Recent Trends in the Regulation of Biopharmaceuticals in Korea

CMC Strategy Forum Japan 2019

11 Dec, 2019

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National Institute of Food and Drug Safety Evaluation (NIFDS)
Ministry of Food and Drug Safety (MFDS)
Disclaimer

The information presented here reflects the views of the presenter and should not be construed to represent MFDS' views or policies.
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   - Current Status of Development & Approvals

II. Updates on Regulatory Framework for Biopharmaceuticals in Korea
    - Changes in organization, laws, and guidelines
    - Support programs

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I. Updates on Biopharmaceuticals in Korea

- Current Status of Biosimilar (as of Oct, 2019)
- Current Status of Cell therapy products (as of Oct, 2019)
- Current Status of Gene therapeutic products (as of Oct, 2019)
1. Recombinant Protein Products

  ✓ 2018
    - NME 4 (mAb 3 / GLP-2 analog 1)
      : Dupixent(dupilumab), Tremfya(guselkumab),
        Imfinzi(durvalumab), Gattex(teduglutide)
    - Biosimilar 2
      : Nesbell(darbepoetin alfa), Eucpect(etarnercept)
  ✓ 2019(~Oct)
    - NME 5 (mAb 4 / ADC 1) (including 2 orphan drugs)
      : Emgality(galcanezumab), Evenity(romosozumab),
        Fasenra(benralizumab),
        Besponsa(inotuzumab ozogamicin), Hemlibra(emicizumab)
    - Orphan 1 : Bavencio(avelumab)
    - Biosimilar 1 : Terrosa(teriparatide)
1. Recombinant Protein Products

• **INDs in Korea**
  ✓ Status of IND approval (Chemical + Bio + Herbal) in Korea
    - Increase of early phase studies (211 phase 1)
    - Increase of studies for severe and rare refractory diseases
    - Increase of studies for biopharmaceuticals
  ✓ Of 679 approvals in 2018
    - Oncology 36 % : target 45.0 %, immuno 37.2 %
    - chemical 61 %,
      • **Recombinant protein products** 26 %,
      • **Cell therapy products** 3.4 %,
      • **Gene therapy products** 1.5 %

*(Reference: IND approvals in 2018 sourced from Clinical Trial Management Division, Feb, 2018)*
1. Recombinant Protein Products

- Clinical Development Status of Recombinant Protein Products in 2019 (Jan~Oct, 2019)

  ✓ Submission : 575

  - 518 (mAb & related products such as Cept) (90 %)
    - Anti-cancer: 383 (74 %)
    - Immune modulator: 73 (14 %)
  - In anti-cancer drugs
    - Immune check point molecules: 180 (47 %)
    - Increase of Engineered mAb, ADC, bispecific mAb, etc.
2. Biosimilar (~2019.10)

- **Approved products (as of March, 2019)**
  - 10 products by domestic companies
  - 4 products by foreign companies

- **Popular Reference Products from INDs & NDAs**
  - Remicade, Humira, Enbrel
  - Herceptin, Mabthera, Avastin
  - Lucentis, Eylea
  - Soliris
  - NESP, (Eprex)
  - Neulasta
  - Lantus, Humalog
  - Gonal-F
  - Forsteo
## 2. Biosimilar (~Oct, 2019)

- **9 Biosimilar products developed by Domestic companies**

<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>Etoloe 50mg</td>
<td>Etanercept**</td>
<td>Rheumatoid Arthritis, Psoriasis</td>
<td>Sep 7, 2015</td>
<td>Benepali (Jan 14, 2016)</td>
<td>-</td>
</tr>
</tbody>
</table>

* PMDA approved
** HC approved
## 2. Biosimilar (~Oct, 2019)

<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>
</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>Eucept* Prefilled Syringe</td>
<td>Etarnercept</td>
<td>RA, Psoriatic Arthritis, etc</td>
<td>Mar 16, 2018</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Chonkundang</td>
<td>Nesbell*</td>
<td>Darbepoetin alfa</td>
<td>Treatment of anemia</td>
<td>Nov 29, 2018</td>
<td></td>
</tr>
</tbody>
</table>

* PMDA approved
** HC approved
### 2. Biosimilar (~ Oct, 2019)

- 4 Biosimilar products developed overseas

<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>Scigen</td>
<td>SciTropin A</td>
<td>Somatropin</td>
<td>Growth hormone deficiency, etc.</td>
<td>Jan 28, 2014</td>
</tr>
<tr>
<td>2</td>
<td>Lilly</td>
<td>Basaglar</td>
<td>Insulin glargin</td>
<td>Diabetes</td>
<td>Nov 25, 2015</td>
</tr>
<tr>
<td>3</td>
<td>Green Cross (Biocon)</td>
<td>Glarzia</td>
<td>Insulin glargine</td>
<td>Diabetes</td>
<td>Mar 07, 2018</td>
</tr>
<tr>
<td>4</td>
<td>Daewon (GedeonRichter plc.)</td>
<td>Terrosa</td>
<td>Teriparatide</td>
<td>Osteoporosis</td>
<td>Oct 29, 2019</td>
</tr>
</tbody>
</table>
3. Cell Therapy Products

- Approved Clinical Trials (as of Oct. 2019)

![Bar chart showing approved clinical trials from 2001 to 2019 for SIT and IIT cell therapies.]

<table>
<thead>
<tr>
<th>Clinical trial No.</th>
<th>Cell Type</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stem Cell</td>
<td>Immune Cell</td>
<td>Somatic Cell*</td>
<td>Xenogeneic Cell</td>
<td></td>
</tr>
<tr>
<td>SIT</td>
<td>177</td>
<td>109</td>
<td>41</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>IIT</td>
<td>121</td>
<td>72</td>
<td>40</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>298</td>
<td>181</td>
<td>81</td>
<td>34</td>
<td>2</td>
</tr>
</tbody>
</table>

*keratinocytes, fibroblasts, chondrocytes, osteoblast, etc.*

(By Kyung-Suk Choi from Cell and Gene Therapy Products Division)
## Market Authorization of Cell Therapy Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Year</th>
<th>Conditional Approval</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stem Cell Products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuronata-R Inj.</td>
<td>2014</td>
<td>Orphan</td>
<td>Amyotrophic Lateral Sclerosis</td>
</tr>
<tr>
<td>Cupistem</td>
<td>2012</td>
<td>Orphan</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Cartistem</td>
<td>2012</td>
<td></td>
<td>Knee cartilage repair</td>
</tr>
<tr>
<td>Hearticellgram-AMI</td>
<td>2011</td>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td><strong>Immune Cell Products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ImmuneCell-LC</td>
<td>2007</td>
<td>Cancer</td>
<td>HCC</td>
</tr>
<tr>
<td>CreaVax-RCC</td>
<td>2013</td>
<td></td>
<td>RC (Export only)</td>
</tr>
<tr>
<td><strong>Somatic Cell Products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cartilife</td>
<td>2019</td>
<td>autologous chondrocytes</td>
<td>Articular cartilage defect of knee</td>
</tr>
<tr>
<td>Rosmir</td>
<td>2017</td>
<td>autologous skin cells</td>
<td>Nasojugal groove</td>
</tr>
<tr>
<td>KeraHeal-Allo</td>
<td>2015</td>
<td></td>
<td>Burn wounds</td>
</tr>
<tr>
<td>Cure-skin</td>
<td>2011</td>
<td>autologous skin cells</td>
<td>Acne scar</td>
</tr>
<tr>
<td>Queencell (min. manipulation)</td>
<td>2010</td>
<td></td>
<td>SC adipose tissue deficiency</td>
</tr>
<tr>
<td>RMS ossron</td>
<td>2009</td>
<td></td>
<td>Local bone formation</td>
</tr>
<tr>
<td>KeraHeal</td>
<td>2006</td>
<td>autologous skin cells</td>
<td>Burn wounds</td>
</tr>
<tr>
<td>Kaloderm</td>
<td>2005</td>
<td></td>
<td>Burn wounds</td>
</tr>
<tr>
<td></td>
<td>2010</td>
<td></td>
<td>Diabetic foot ulcer</td>
</tr>
<tr>
<td>Holoderm</td>
<td>2002</td>
<td>autologous skin cells</td>
<td>Burn wounds</td>
</tr>
<tr>
<td>Chondron</td>
<td>2001</td>
<td>autologous chondrocytes</td>
<td>Articular cartilage defect</td>
</tr>
</tbody>
</table>

As of Oct. 2019
4. Gene Therapy Products

• Approved Clinical Trials (as of Oct. 2019)

Vector type

<table>
<thead>
<tr>
<th>Plasmid</th>
<th>Adenovirus(AV)</th>
<th>AAV</th>
<th>Plasmid +AV</th>
<th>Vaccinia virus</th>
<th>mRNA</th>
<th>Retrovirus</th>
<th>HSV</th>
<th>Bacteria</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vivo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>55</td>
</tr>
<tr>
<td>Ex vivo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td></td>
<td></td>
<td>19</td>
</tr>
</tbody>
</table>

(By Kyung-Suk Choi from Cell and Gene Therapy Products Division)
II. Updates on Regulatory framework for Biopharmaceuticals in Korea
1. Organization

- Launched the Convergence Innovation Product Support Division (Mar 2019)
  - Main duties: Receipt & Approval of MA submission
  - Purpose: For improvement of communication between reviewers and applicants (industry)
  - Key mission for 2019
    A. Enhancement of Transparency and Predictability of Procedures
      - Pre-Receipt assessment for Improving quality of submissions
      - Management of review procedures and duration (including oral presentation, day-80 meeting, etc.)
      - Introduction of a standardized format for deficiency letter (including detailed descriptions of the reasons for the supplement and the regulatory basis.)
    B. Disclosure of Approval and Review Information in Standardized Format
    C. Development and Implementation of plans for revision of regulations on biopharmaceuticals (Certificate/Document)
      - Orphan drugs, blood products, accompanied materials such as WFI, etc.
Biopharmaceuticals Review Management Division was launched!

Purpose:
To create frameworks to secure safety of advanced regenerative medicine and develop measures to support technological innovation in this field and subsequent utilization, and

To provide well-established provisions and guidance necessary to secure quality, safety and efficacy of advanced biopharmaceuticals and support their commercialization,

→ thereby contributing to improving public health and quality of life of the people.
Clinical research will be classified based on their potential impact on human life and health as low, medium, & high-risk trials. Among them, high-risk trials will still need approval by the MFDS as the current regulatory scheme requires.
<table>
<thead>
<tr>
<th>Item</th>
<th>New Legislation</th>
<th>Regulation on Review and Authorization of biological Products (MFDS Notification)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope</td>
<td><strong>Article 36 (Designation for Expedited Procedure)</strong> ① One of the following should apply: 1. Treatment for serious diseases, such as cancer that is life-threatening, and no alternative therapeutic option is available for, 2. Treatment for rare diseases, or 3. Prevention against and treatment for bioterrorism-related infectious diseases and other pandemic infectious diseases.</td>
<td><strong>Article 24 (Waiver of Data Submission, etc.)</strong> ② Orphan drugs ③ Anticancer drugs, etc. ④ Cell therapy products for the treatment of life-threatening or severe, irreversible diseases</td>
</tr>
<tr>
<td></td>
<td>Annex 2 9. Cell therapy products that contain autologous chondrocytes or autologous skin cells as an active ingredient</td>
<td></td>
</tr>
</tbody>
</table>
3. Guidelines


  ✓ As a guideline of the MFDS containing the contents of ICH Q5E, frequently-occurring changes are classified as major and minor, and specific data requirements are assigned for each change, taking into account international harmonization.

  ✓ Main revision point: description examples of marketing authorization (manufacturing process)
    - Currently conducting discussion with the industry.
    - Adjustment of described items by distinguishing what should be reported to the MFDS and what is managed by the manufacturer according to GMP.
3. Guidelines

- Guideline on Immunogenicity Assessment of Therapeutic Proteins (revised in Dec. 2019)
  - Purpose: Harmonization with relevant global guidelines
  - Main revision point
    - Clarification of Scope (excluding vaccines)
    - Additional considerations for nonclinical evaluation of immunogenicity
    - Additional considerations in selecting antibody test methods
    - Information on sampling for immunogenicity evaluation in clinical trials
    - Comparative immunogenicity assessment in biosimilar development and evaluation
    - Added immunogenicity assessment in post-marketing pharmaco-vigilance
4. Support Program for Domestic Companies

<Name : Majung-Mul Program>

- Aims: to support the development of domestic recombinant protein products
- Target: products entering the nonclinical and clinical phases
- Regular consultation with developers on development plans, and regulatory requirements for each developmental stage
- Results (~2019): 10 products by 10 domestic companies
  - mAb (5) / ADC (1) / bispecific mAb (1) / other therapeutic proteins 3
  - anti-cancer drugs (8) / macular degeneration (1)
  - antibiotic-resistant bacterial infection (1)
5. Consultation services

<Prior-review>

- Consultation services
  ✓ Review & meeting period: ~ 50 days
  ✓ Feedback provided on questions
  ✓ Face-to-face meeting if requested

- Review of Unit Submissions: review of Unit Documentation required for drug approval
  ✓ CMC review: New product/120 days, Changes/30 days
  ✓ Safety/Efficacy review: New product/60 days, Changes/45 days
  ✓ Others: 50 days
III. Regulator’s Perspective on Key Considerations for CMC Assessment of Biopharmaceuticals (specifically focusing on recombinant protein products)
1. Biosimilar

☐ Bridging data requirement

when developed using a foreign reference product

✓ Basically, 3-way (foreign RP – Korea RP – Biosimilar) analytical comparability studies are required.

✓ Extensive comparability studies

- Comparative Characterization + Forced Degradation studies
  (Approximately the same items as comparability studies conducted as main studies)

✓ In case of Korean RPs, it is generally recommended to evaluate more than three batches by obtaining them in order to take into account the variability between batches at different times of manufacture.

*Refer to Q & A on Biosimilar Evaluation (revised in Dec. 2018)
1. Biosimilar

- **Requirements for the batch to be analyzed**
  
  - **Biosimilar batches**
    - Should be performed for to-be-commercial batches of biosimilar.
    - Predominately analyzed in DP lots, but certain parameters can be analyzed in DS lots (DS lots should be representative of DP lots appropriately).
  
  - **Reference product**
    - Should include the batches used in the nonclinical and clinical studies.
    - Continued analysis during the biosimilar development (with sourcing strategies such as when to buy, when to analyze, where to buy).
    - Should provide the batch information analyzed for Analytical Comparability Assessment.

*Refer to Q & A on Biosimilar Evaluation (revised in Dec. 2018)*
또한, 비교동등성시험에 사용된 동등생물의약품과 대조약은 상품명, 제형, 조성, 용량, 
대조약의 줄지, 사용된 배치 수, 배치번호, 제조일(또는 사용기간) 등이 명확히 
확인되어야 합니다.

제출자료의 작성 양식은 아래 예시를 참고하시기 바랍니다.

[예시] 동등생물의약품 비교동등성 제출자료 요약

<table>
<thead>
<tr>
<th>구분</th>
<th>상품명 (구매출처)</th>
<th>제형</th>
<th>조성</th>
<th>용량</th>
<th>배치수 (배치번호)</th>
<th>제조일 (사용기간)</th>
<th>사용 목적</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>
1. Biosimilar

**Acceptance Similarity Criteria**

- We have generally accepted various statistical acceptance criteria, ranging from mean ± 2SD/3SD to tolerance interval, prediction interval, and equivalence testing. Basically, the applicant must justify the selected statistical approach, such as the comparison of various forms of statistical approaches and data.

- In addition, we have determined the final analytical comparability by taking into account the representative of the reference product batches, the analytical methods capability, and the impact on safety or efficacy.

- If the distribution range and mean values of data between Biosimilar and Reference product are found to differ from each other, it is necessary to analyze the root cause and submit the result of the investigation as to if it is located within the comparability acceptable interval.
2. Common Issues on Stability Data

□ Considerations of stability data requirements not defined in national and international guidelines

* Consequently, there exist some differences b/t national regulatory requirements.
* In 2019, we shared relevant cases and discussed with the industry on the following topics.

✓ Flexible application of bracketing design to biopharmaceuticals
✓ Labelling and supporting data requirements of ‘In-use hold condition’ for single-use injections for IV infusion
✓ Intermediate Hold times
✓ The impact of temperature excursions & light exposure during manufacturing & distribution
2. Common Issues on Stability Data

A. Flexible application of bracketing design to biopharmaceuticals

Rigorous interpretation of ICH Q5C allowed the application of bracketing only to cases of three or more filling volumes as liquid formulations, and not to lyophilized powder products. (There have been cases where the bracketing approach was approved for liquid of different concentration or lyophilized powder products.)

ICH Q1D & Q5C

- Q1D: extremes of certain design factors (e.g., strength, container size and/or fill)
- Q5C: Where the same strength and exact container/closure system is used for 3 or more fill contents

* Difference in the use (definition) of strength??
2. Common Issues on Stability Data

B. Labelling and supporting data requirements of ‘In-use hold condition’ for single-use injections for IV infusion

There are differences in the data requirements, with different labeling requirements for different regulatory authorities (Europe, the US, Korea) regarding the establishment of in-use conditions for single-use injections administered by IV infusion after dilution/reconstitution.

In Korea, we consider the results of the physicochemical stability as well as the microbiological safety assessment (spiking study), and require description of the condition (temperature & period) on the label that is considered appropriate (safety margin is considered).

In Korea, we have only one relevant guideline published; ‘Guideline on Aseptic Operation of Injections’ <for Medical staff>.
2. Common Issues on Stability Data

C. Intermediate Hold times

No clear requirements of stability studies (testing items, hold time, cumulative approach, etc.) to determine intermediate hold times.
2. Common Issues on Stability Data

D. The impact of room temperature & light exposure during manufacturing & distribution

Based on understanding of the stability profile of the product, assessment is needed to minimize the effect of manufacturing process conditions on quality.

In particular, the drug product manufacturing process is susceptible to exposure to room temperature and visible light conditions, so in case of unstable products, evaluation for process development is required (in case of light exposure, it is more relevant to consider the light conditions of the actual work place than the ICH Q1B conditions.)
3. Other CMC Issues

**CCIT**

✓ Increasing demand for Routine monitoring of Container-closure integrity

✓ In Korea, strongly recommended to domestic companies.

✓ Regulatory requirements will be determined in accordance with changes in global regulatory requirements such as GMP regulations and guidelines.

**Extractables/Leachables**

✓ Request for evaluation data on DS / DP container

✓ Strongly evaluation required on materials used during the manufacturing process.
4. New Trends

New technologies

✓ Continuous Manufacturing, Big data, Automation extension
✓ Expansion of commercially used expression systems (ex. plant)
✓ Advances in drug delivery technologies and devices

New technologies raise new regulatory challenges.

2. Accelerated Development

✓ Personalized, Precision Medicine / Rare diseases (Orphan drugs)
✓ Rapid development of new (type/class of) products through technological innovation

Less data over short development periods,

What are the regulatory requirements for ensuring quality?

Can we be flexible with our regulatory requirements?
IV. Summary
The development and approval of biopharmaceuticals in Korea continues to increase, and the biotechnology industry in Korea is expected to continue to grow.

In case of Recombinant protein products, biosimilars are the main focus, but the development of new drug candidates, such as immune check point mAb, bispecific mAb and new types/classes products, is also increasing.

A total of 16 cell therapy products have been approved to date and over 90 clinical trials are in progress.

Development of gene therapy products is increasing.
We will introduce a new regulatory framework for systematic control based on the characteristics of regenerative medicines to provide expanded access to better treatments for patients.

In addition, some examples of issues raised during MFDS CMC review are presented. Regulatory requirements that raise uncertainty in drug development make the process less efficient. Therefore, scientifically sound regulatory requirements need to be clearly stated to ensure a high level of quality without unnecessary burden.
The key point is collaboration & harmonization.

Through collaboration between industries and global regulators, it will be possible to establish clear regulatory requirements or to address various issues that arise.

The MFDS is constantly working to increase procedural transparency and predictability, and will continue to promote international harmonization and clarification of regulatory standards, including ICH member activities and WHO cooperative activities. We hope this will play a positive role in the global bio industry.
Thank you for your attention

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NIFDS, MFDS

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