Regulatory policy directions for cell and gene therapy products

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NIFDS/MFDS
Structure of legislations for cell & gene therapy products

- Pharmaceutical Affairs Act
- Enforcement Rules of the Safety of Pharmaceuticals
- Notification on Review and Authorization of Biological Products
- Guideline on the Requirements for Quality Documentation of Cell Therapy Products
- Guidance on Sponsor-Investigator Trials of Cell Therapy Products for Academic Purpose, etc.
MFDS guidelines for cell & gene therapy products

- Considerations for Evaluation of Dendritic Cell Therapy Products for Cancer Treatment (2005)
- Guideline on Mycoplasma Test Suitable for Cell Therapy Products (2008)
- Considerations for Validation of Quantitative Polymerase Chain Reaction Method for Bio-distribution study
- Guideline on Characterization of Cell Substrates Used to Produce Biological Products (2010)
- Guideline on Adventitious Virus Test for Biological Products for Human Use (2010)
- Guideline on Validation of Polymerase Chain Reaction Method for Mycoplasma Test of Cell Therapy Products (2012)
- Guideline on Manufacture and Quality Control of Cell Therapy Products (2012)
- Guideline on testing for Quality Control of Cell therapy products(2014)
- Guideline on preclinical assessment of stem cell products(2014)
- The others

* And abide by ICH and other relevant guidelines
Definition of Cell Therapy Products

- A medicinal product manufactured through physical, chemical, and/or biological manipulation, such as *in vitro* culture of autologous, allogeneic, or xenogeneic cells
- Exemption: where a medical doctor performs minimal manipulation which does not cause safety problems of autologous or allogeneic cells in the course of surgical operation or treatment at a medical center (simple separation, washing, freezing, thawing, and other manipulations, while maintaining biological properties) (*MFDS notification Article 2*)

Examples of minimal manipulation include,

1. Separation; A process of ficoll density-gradient separation or centrifugation
2. Selection
3. freezing, thawing, washing and etc.
Definition of Gene Therapy Products

A medicinal product which contains either

- Genetic material to influence the gene expression
- Genetically modified, or genetic material-transduced cells

(MFDS notification Article 2)

Approval Scopes of Gene Therapy Products (MFDS notification Article 3)

1. If it is intended for treatment of genetic disease, cancer, AIDS, or other conditions that may be life-threatening or result in serious disorders.
2. If an appropriate therapy is not available or it is possible to predict that the effectiveness of a gene therapy product is superior to other available therapies.
3. Others deemed necessary for prevention or treatment of diseases by the minister of MFDS
### Regulation of Cell & Tissue based Products in Korea

<table>
<thead>
<tr>
<th>Cell</th>
<th>Manufacturing</th>
<th>Autologous</th>
<th>Allogeneic</th>
<th>Xenogeneic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal manipulation</td>
<td>at a medical center</td>
<td>Medical Practice <em>(Medical Service Act)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outside the medical center</td>
<td></td>
<td></td>
<td>Biologics <em>(Pharmaceutical Affairs Act)</em> : Cell therapy products</td>
<td></td>
</tr>
<tr>
<td>More than minimal manipulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Tissue

<table>
<thead>
<tr>
<th></th>
<th>Medical Practice <em>(Medical Service Act)</em></th>
<th>Human tissues <em>(Human Tissue Safety &amp; Control Act)</em></th>
<th>Medical Device <em>(some of products like porcine valve. Medical Device Act)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tissue-Engineered Products <em>(Biologics or Medical Device)</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Organ

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Human organs for transplantation <em>(Organs transplantation Act)</em></td>
<td></td>
</tr>
</tbody>
</table>

- Cord blood: *Umbilical Cord Blood Control and Research Act*
- Blood products: *Blood Management Act*
- Human derived cell & tissue: *Bioethics and Safety Act*
- Human tissues regulated under HTSCA: cartilage, bone, ligament, tendon, skin, heart valves, blood vessel, fascia, amnion etc
Current regulatory activity
First cell therapy product: Chondron (2001)

WHO PQ vaccine: Euvax B (1996)

First, FDA-approved blood coagulation factor VIII (1966)

First, FDA-approved antibody drug: OKT3 (1986)

First, FDA-approved recombinant product: insulin (1982)

First, FDA-approved biochip: AmpliChip CYP450 (2004)

First, EMA-approved gene therapy product: Glybera (2012)

First, anticancer immune therapy: Immuncel-LC (2007)

The first stem cell products:
- Hearticellgram (2011)
- Cartistem, Cupistem (2012)

Biosimilar mAb products
- Remsima (2012)
- Herzuma (2013)
### Regulatory Activities of cell therapy products

#### Market Authorization (as of June, 2017)

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Cell &amp; Manipulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Stem cell</td>
</tr>
<tr>
<td>14</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Approved Clinical Trials (as of June, 2017)

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Company (Medical Institute)</th>
<th>Cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Stem cell</td>
</tr>
<tr>
<td>SIT</td>
<td>136</td>
<td>81</td>
</tr>
<tr>
<td>IIT</td>
<td>106</td>
<td>63</td>
</tr>
<tr>
<td>Total</td>
<td>242</td>
<td>144</td>
</tr>
</tbody>
</table>

* keratinocytes, fibroblasts, chondrocytes, osteoblasts
# Authorized cell therapy products

## 1. Stem cell products

<table>
<thead>
<tr>
<th></th>
<th>Product</th>
<th>Active Substance</th>
<th>Approval date</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neuronata-R injection</td>
<td>MSC (auto./bone marrow-derived)</td>
<td>July 30, 2014</td>
<td>Corestem</td>
<td>Amyotrophic Lateral Sclerosis (Lou Gehrig’s disease)</td>
</tr>
<tr>
<td>2</td>
<td>Cupistem</td>
<td>MSC (auto./fat-derived)</td>
<td>Jan. 18, 2012</td>
<td>Antrogen</td>
<td>Anal fistula from Crohn’s disease</td>
</tr>
<tr>
<td>3</td>
<td>Cartistem</td>
<td>MSC (allo./cord blood-derived)</td>
<td>Jan. 18, 2012</td>
<td>Medipost</td>
<td>Knee cartilage repair of degenerative or repetitive traumatic osteoarthritis</td>
</tr>
<tr>
<td>4</td>
<td>Hearticellgram-AMI</td>
<td>MSC (auto./bone marrow-derived)</td>
<td>July 1, 2011</td>
<td>Pharmicell</td>
<td>Left ventricular ejection fraction in myocardial infarction patients</td>
</tr>
</tbody>
</table>

## 2. Immune therapy

<table>
<thead>
<tr>
<th></th>
<th>Product</th>
<th>Active Substance</th>
<th>Approval date</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Immunecell-LC</td>
<td>Activated T-lymphocyte</td>
<td>Aug. 6, 2007</td>
<td>Green Cross Cell</td>
<td>Liver cancer</td>
</tr>
<tr>
<td>2</td>
<td>CreaVax-RCC</td>
<td>Dendritic cell (autologous)</td>
<td>Dec. 26, 2013</td>
<td>JW CreaGene</td>
<td>Metastatic renal cancer (for export only)</td>
</tr>
</tbody>
</table>
## Authorized cell therapy products

### 3. Somatic cell therapy

<table>
<thead>
<tr>
<th></th>
<th>Product</th>
<th>Active Substance</th>
<th>Approval date</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KeraHeal-Allo</td>
<td>Keratinocyte (allo./skin-derived)</td>
<td>Oct. 16, 2015</td>
<td>Biosolution</td>
<td>Deep 2nd degree burns (skin regeneration)</td>
</tr>
<tr>
<td>2</td>
<td>Cure-skin</td>
<td>Fibroblast (autologous)</td>
<td>Oct. 5, 2011</td>
<td>S-biomedics</td>
<td>Alleviation of depressed fibrotic scars</td>
</tr>
<tr>
<td>3</td>
<td>Queencell</td>
<td>MM adipocyte (auto./ adipose tissue-derived)</td>
<td>Mar. 26, 2010</td>
<td>Antrogen</td>
<td>MM adipocyte (auto./ adipose tissue-derived)</td>
</tr>
<tr>
<td>4</td>
<td>RMS ossron</td>
<td>Osteocyte (autologous)</td>
<td>Aug. 26, 2009</td>
<td>Sewon Cellontech</td>
<td>Local bone formation (enhancing reconstruction)</td>
</tr>
<tr>
<td>5</td>
<td>KeraHeal</td>
<td>Keratinocyte (human)</td>
<td>May 3, 2006</td>
<td>Biosolution</td>
<td>Treatment of burn wounds</td>
</tr>
<tr>
<td>6</td>
<td>Kaloderm</td>
<td>Keratinocyte (human)</td>
<td>Mar. 21, 2005</td>
<td>Tego Science</td>
<td>Burn wounds Diabetic foot ulcer</td>
</tr>
<tr>
<td>7</td>
<td>Holoderm</td>
<td>Keratinocyte (autologous)</td>
<td>Dec. 10, 2002</td>
<td>Tego Science</td>
<td>Treatment of burn wounds</td>
</tr>
<tr>
<td>8</td>
<td>Chondron</td>
<td>Chondrocyte (autologous)</td>
<td>Jan. 30, 2001</td>
<td>Sewon Cellontech</td>
<td>Articular cartilage defect (knee) Articular cartilage defect (ankle)</td>
</tr>
</tbody>
</table>
### Approved Clinical Trials: GT as vector type (as of June 2017)

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Company</th>
<th>Product</th>
<th>In vivo</th>
<th>Ex vivo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Plasmid</td>
<td>Adenovirus</td>
</tr>
<tr>
<td>57</td>
<td>27</td>
<td>28</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Regulatory Activities of gene therapy products**
3 Regulatory policies
MFDS Regulatory approach for biological products

**Offer Therapeutic Opportunities**
- Emergency/Treatment IND
- Conditional authorization
  - anti-cancer drugs
  - orphan drugs
  - cell therapy products with certain conditions
- Enforcing the Scientific advice
- Accelerated review
  - Life threatening disease
  - No available therapy exist
  - Bioterrorism, pandemic vaccines
  - Significantly advanced in safety and efficacy in severe disease
- Majungmul Program

**Ensure Safety of the Patients**
- Re-examination of drug
  - Active surveillance of adverse events and efficacy endpoints after 4 ~6 years of marketing period
- Risk Management Plan
  - Safety reporting for every use of approved stem cell therapy products
  - Long-term follow-up reporting for the patients enrolled in stem cell therapy and in gene therapy
Conditional authorization of cell therapy products

- Eligible to file with exploratory clinical data (No exemption in quality and non-clinical data)
- Marketing condition
  - Submission of confirmatory clinical data after certain time period of marketing authorization date
- Scope
  1. Autologous skin cells or chondrocyte
  2. Cell product with life-threatening or severe irreversible disease and its exploratory trial should properly surrogate confirmatory trial
Pre-requisite for conditional authorization of cell therapy products

- **Disease scope (life-threatening or severe irreversible)**
  - Consulted with scientific advisory group

- **Exploratory clinical trial**
  - Controlled, randomized, blinded, comparative
  - Efficacy endpoint should use well-defined surrogate endpoint or intermediate clinical endpoint that represent confirmatory endpoint

- **RMP**
  - Complete enumeration study for 2 years after marketing
  - Marketing available only in designated hospital, off-label use prohibited, and patient informed consent required
Pre-requisite for conditional authorization of cell therapy products

• Post-marketing commitment
  ✓ Conduct of phase3 trial and annual written report
  ✓ The time period determination should based on prevalence of the disease, efficacy evaluation period, and clinical subject number.
  ✓ Regular reporting of risk management status

• Phase3 clinical trial
  ✓ Close consultation with CGTP Division on phase3 trial design from early application stage of conditional authorization
  ✓ Design requirements: blind, randomized, well-controlled, multi-center trial. Endpoint should reasonably predict clinically benefit
Majungmul(Priming water) Project
- Scientific advice program for facilitating innovative biological products

- addressing regulatory hurdles and difficulties for pursuing marketing authorization

**Product based and tailored consultation for the product in late phase of development**
: team consisting of regulatory experts

1. Educating researchers for basics in regulatory requirements
   : biannual training program

2. Open communication from early phase of development
   : monthly consultation day (every Wednesday of last week)

- collaborative work with governmental org.
- regulatory consultation with developers who do not have regulatory experience
Conclusion

- MFDS have authorized 14 cell therapy products, which rank top in the global market. Attention is being paid in the adult stem cell clinical development
- Especially development of gene therapy products is increasing
- To play as an enabler of medicine development, MFDS implemented new regulatory policy such as conditional authorization of cell therapy products of which indications are life threatening or severe and irreversible disease but at the same time MFDS strengthen the RMP to protect patient’s safety
- MFDS will continue to enforce our competency by strengthen our regulatory expertise and international collaboration
THANK YOU!

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