Regulatory Update on Cell and Gene therapy products in Korea

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Contents

- Cell & gene therapy product regulation
- Current status on cell & gene therapy products
- Supporting development of cell & gene therapy products
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)

Specific examples of minimal manipulation include,

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

※ Proliferation of cells as a result of cell culturing, cell activation using growth factors and gene transduction are not included in the above scope of minimal manipulation.
Definition of Gene Therapy Products

A genetic material or a medicinal product containing such genetic material intended to be administered into a human body for treatment of disease *(MFDS notification Article 2)*

Approval Scopes of Gene Therapy Products

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 Commissioner of the KFDA.
# 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</td>
<td>at a medical</td>
<td>Medical Practice</td>
<td>Medical Practice</td>
<td>Biologics</td>
</tr>
<tr>
<td>manipulation</td>
<td>center</td>
<td>(Medical Service Act)</td>
<td>(Medical Service Act)</td>
<td>(Pharmaceutical Affairs Act)</td>
</tr>
<tr>
<td>Outside</td>
<td></td>
<td></td>
<td></td>
<td>: Cell therapy products</td>
</tr>
<tr>
<td>the medical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>center</td>
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</tr>
<tr>
<td>More than</td>
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</tr>
<tr>
<td>minimal</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>manipulation</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tissue</td>
<td>Medical Practice</td>
<td>Human tissues for transplantation</td>
<td>Medical Device</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Medical Service Act)</td>
<td>(Human Tissue Safety &amp; Control Act)</td>
<td>(some of products like porcine valve. Medical Device Act)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tissue-Engineered Products</td>
<td>(Biologics or Medical Device)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ</td>
<td>-</td>
<td>Human organs for transplantation</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Internal Organs, etc. Transplant Act)</td>
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</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
Lifecycle Regulation of Cell & Gene Therapy Products

I. DEVELOPMENT
- GCP, GLP, GMP
- IND (30 days review)
- Orphan drug designation
- Pre-review

II. PRODUCT LICENSING (115 days review)
- Quality
- Safety and Efficacy
- Pre-approval GMP/GCP inspection

III. MARKETING & UTILIZATION
- Re-evaluation
- Re-examination
- PSUR
- Risk management plan
- Periodic or for-cause inspection (GMP, GIP)
- Advertisement monitoring
- GDP, GSP
- Patent listing
- Product license renewal (5 yrs)

- Application fee: $3,730 for new drug application
- CTD submission since 2009
- Website: http://ezdrug.mfds.go.kr
### Regulatory Activities

**Currently Approved Cell Therapy Products**

<table>
<thead>
<tr>
<th>Products no.</th>
<th>Company no.</th>
<th>Cell &amp; Manipulation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Stem cell</td>
</tr>
<tr>
<td>14</td>
<td>10</td>
<td>4</td>
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</table>

**Approved Clinical Trials for Cell Therapy Products**

<table>
<thead>
<tr>
<th>No of</th>
<th>Clinical trials.</th>
<th>Sponsors</th>
<th>Cell type</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td>Stem cell</td>
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<tr>
<td>SIT</td>
<td>116</td>
<td>30</td>
<td>63</td>
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<tr>
<td>IIT</td>
<td>88</td>
<td>29</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>204</td>
<td>59</td>
<td>111</td>
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</tbody>
</table>

*keratinocytes, fibroblasts, chondrocytes, osteoblasts

**Approved Clinical Trials for Gene Therapy Products**

<table>
<thead>
<tr>
<th>Clinical trials</th>
<th>Sponsors</th>
<th>Vector types</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Plasmid</td>
</tr>
<tr>
<td>43</td>
<td>20</td>
<td>18</td>
</tr>
</tbody>
</table>
### 14 Cell therapy products are authorized (as of February 2016)

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondrocyte (auto) (1)</td>
<td>Articular cartilage defects (Knee)</td>
</tr>
<tr>
<td>Keratinocyte (auto/allo) (4)</td>
<td>Burn wounds, Diabetic foot ulcer</td>
</tr>
<tr>
<td>Fibroblast (auto) (1)</td>
<td>Treatment of acne scar</td>
</tr>
<tr>
<td>Osteoblast (auto) (1)</td>
<td>Acceleration of bone formation</td>
</tr>
<tr>
<td>Dendritic cell (auto) (1)</td>
<td>Metastatic renal-cell carcinoma</td>
</tr>
<tr>
<td>Activated lymphocyte (auto) (1)</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Adipose cell (minimally manipulated) (1)</td>
<td>Subcutaneous fat defect</td>
</tr>
<tr>
<td>Bone marrow-derived MSC (auto) (2)</td>
<td>Improvement of left ventricular ejection fraction (AMI)</td>
</tr>
<tr>
<td>Umbilical cord blood-derived MSC (allo) (1)</td>
<td>Articular cartilage defects (Knee)</td>
</tr>
<tr>
<td>Adipose-derived MSC (auto) (1)</td>
<td>Complex perianal fistula (Crohn’s disease)</td>
</tr>
<tr>
<td></td>
<td>Delay of amyotrophic lateral sclerosis (ALS)</td>
</tr>
<tr>
<td></td>
<td>Delay of amyotrophic lateral sclerosis (ALS)</td>
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</table>
Specific Consideration - Quality

• **Maintenance of aseptic condition**
  - final products are living cells, maintenance of aseptic condition in manufacturing process is critical
  - human & animal origin materials in manufacturing ⇒ strict microbiological control

• **Short shelf-life**
  - some QC testing cannot be completed before releasing
    → in-process testing with representative samples
    → development of alternative testing method
    → investigation plan in case microbiology test is positive

• **Limited production - small batch size**
  - not enough samples for QC testing ⇒ in-process control

• **Subject-to-subject variation in cell source**
  → establishment of minimal criteria to ensure safety, efficacy, consistency of product
    (ex. phenotype, genotype, synthesis of bio-active factors, etc)
Specific Consideration- Preclinical

• **Traditional PK studies are not feasible : cells**
  → appropriate animal species, disease model animals, immuno-deficient animals, large animals, analogous animal cells
  → delivery : represent route of administration and target site in clinical trials
  → hybrid pharmacology-toxicology study design
  → bio-distribution study in combination w/ pharmacology or toxicology study

• **Tumorigenicity study**
  - intended clinical product, route of administration, immune deficient animals
  - study design? appropriate positive and negative control?

- **No sufficient studies to clarify mechanism of actions**
Specific Consideration- Clinical

- **Limited clinical experience**: long-term effect?
  - concern over tumor or ectopic tissue formation
  - maintenance of efficacy
  - long-term follow-up required (duration?, method?)

- **Limitation in extrapolation of preclinical data to clinical design**
  - lack of appropriate pre-clinical assessment system, considerable uncertainty
    → dose selection: body weight, biodistribution profile, feasibility of production and administration, similar clinical experience, etc.
    → staggering administration

- **Administration through surgical procedures**
  - invasive operation may be included
    → delivery design & standardized procedure, operator’s training
    → appropriate study design (placebo?, blinding?)

- **Small cohort size**
  - limited manufacturing capacity, limited patient population, high cost in clinical trial
Re-examination of drug - Active surveillance of adverse events and efficacy endpoints after 4 ~6 years of marketing period

Risk Management Plan (July 2015~)
- Safety reporting for every use of approved stem cell therapy products (July 2015~)
- Long-term follow-up reporting for the patients enrolled stem cell clinical trials (December 2015~)

Emergency IND
Treatment IND
Conditional Approval (NDA)
  - anti-cancer drugs
  - orphan drugs
  - autologous keratinocytes and chondrocytes

Pre-review system (= Scientific advice) → IND or NDA
  - CMC package
  - Pre-clinical and/or clinical data

Offer Therapeutic Opportunities

Ensure Safety of the Patients
Majungmul (Priming water) Project
- Scientific advice program for facilitating innovative biological products

- addressing regulatory hurdles and difficulties for pursuing marketing authorization

Q3
Product based and tailored consultation for the product in late phase of development
: team consisting of regulatory experts

Q1
Educating researchers for basics in regulatory requirements
: biannual training program

Q2
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
Thank you for your attention!