Regulatory Considerations for Cell Therapy Products

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KFDA’s Mission

Prevent and Manage Food and Drug related Risks in Advance

Rapid Response to Food and Drug Safety Risk

Establish Communication network and Support relevant parts

The views expressed in this presentation are my personal views, and may not be understood or quoted as being made on behalf of the KFDA.
Regulation of Cell & Tissue

**Biologics**
*(Pharmaceutical Affairs Act)*
- Manipulated cells & tissues
- Genetically modified cells
- Tissue/cell combined w/ devices, biologics, drugs

**Human Tissue**
*(Human Tissue Safety Control Act)*
- Cartilage, Bone
- Ligament
- Tendon
- Skin
- Human heart valves
- Blood vessel
A medicinal product manufactured through physical, chemical, and/or biological manipulation, such as *in vitro* culture of autologous, allogeneic, or xenogeneic cells.
Exemption:

✓ The case 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)

- Regulation on Review and Authorization of Biological Products -
Examples of Cell Therapy Products

- Implantation of modified tissue specific cell population
  - eg; Islet, Keratinocyte, Chondrocyte

- Introduction of immunogenic cell populations
  - for Immunotherapy (eg; DC, LAK)

- Introduction of stem cell populations
  - mesenchymal, embryonic
Regulatory Framework

3- tiered system

- Law
  - Pharmaceutical affairs Act
- Regulations
  - details of the law
  - Regulation on review and authorization of biological products, etc.
- Guidelines
  - interpretation of the regulations
  - advices, current thinking, not binding on Agency or Industry
Dossier for Clinical Trial: IND

- Schedule for development
- Physicochemical, biological information
- Preclinical data
- Clinical trial protocol
- References
Dossier for Product Evaluation: NDA

- Background of pharmaceutical development
- Structural determination & physicochemical characteristics (CMC)
- Stability data
- Toxicological data
- Pharmacological data
- Clinical study data
- Information on use & authorization in Korea and/or foreign countries
- Other information on characteristics of the medicinal product
1. Backgrounds & Definitions

2. Regulatory Considerations in Korea

3. Cell Therapy Products in Korea
(1) Regulatory Considerations on CMC

- Characterization of cell
- Cell collection and culture
- Cell banking
- Product manufacturing process
- Product testing
✓ Product Safety
  - Donor screening and testing
  - Product testing
    (Adventitious agents, tumorigenicity, pyrogenicity)
  - Biocompatibility testing with device
    (eg; Combination products)

✓ Product Characterization
  - Identity, Purity, Potency, Viability, Stability
  - Phenotype, Gene/protein expression
  - Other than that measured for potency
Manufacturing Process-cGMPs
- Control production & process
- Qualification of reagents
- Segregation & tracking
  (Different donors / different lots)

Reproducibility / Consistency of Products lots
- Development of in-process and lot release specification
Relevant Product Release Tests

- Sterility
- Mycoplasma
- Endotoxin
- Adventitious virus
- Identity
- Purity
- Potency; ideally, quantitative assay
- Others as needed (cell viability, cell number, etc.)
(2) Regulatory Considerations on Non-clinical studies

<table>
<thead>
<tr>
<th>Pharmacological studies</th>
<th>Cell Therapy Products</th>
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<tbody>
<tr>
<td>Pharmacodynamics</td>
<td>△</td>
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<tr>
<td>General pharmacology</td>
<td>△</td>
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<tr>
<td>ADME</td>
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<table>
<thead>
<tr>
<th>Toxicological studies</th>
<th>Cell Therapy Products</th>
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<tr>
<td>Single dose</td>
<td>△</td>
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<tr>
<td>Repeated dose</td>
<td>△</td>
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<tr>
<td>Reproductive &amp; Developmental</td>
<td>△</td>
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<tr>
<td>Genetic toxicity</td>
<td>△</td>
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<tr>
<td>Tumorigenicity</td>
<td>△</td>
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<tr>
<td>Other toxicities</td>
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△ : can be exempted on a case-by-case basis
Issues on pharmacological studies

- Pharmacodynamics: *proof-of-concept*
  - *in vitro and/or in vivo* efficacy data
  - pharmacologically relevant animal model
    (mimic the human response)
  - dose and route of administration planned for clinical trial

- Biodistribution
  - trafficking, persistence of cells
  - ectopic tissue formation (stem cells)
  - PCR, IHC, cell labeling
Issues on toxicological studies

- Single dose toxicity/Repeated dose toxicity:
  - general health status, hematologic profiles,
  - serum biochemistry, histopathologic examination
- Tumorigenicity
- Other toxicity: Local tolerance toxicity,
  - Immunological reactions
Issues on toxicological studies

1) Appropriate animal model should be used

2) Single/repeated tox. :
   - more than one species could be needed
   - observation period
     : treatment duration of clinical trial, biodistribution

3) In case of stem cells and etc, tumorigenicity should be considered

4) In general, genotoxicity study is not required

5) If products are not detected at genital gland and genital organs, the fertility and general reproductive toxicity studies may not be needed

6) Local tolerance studies can be evaluated in single or repeated dose toxicity studies
(3) Regulatory Considerations on Clinical studies

- In general, the same safety requirements as for other medicinal products shall apply.
- For the clinical trial on stem cell, a specific surveillance plan for the assessment of long-term safety and unique risk is recommended.
Conventional ADME studies may not be appropriate however, clinical biodistribution may be important and its absence should be explained.

Immunogenicity should be considered in allogenic or xenogenic origin.
(3) Regulatory Considerations on Clinical studies

✓ In general, the same efficacy endpoint as for other medicinal products shall apply
✓ Provision of evidence for mode of action
  - cell population, molecule secreted, etc
✓ Effective range of cells administered should be defined or justified
The conventional clinical study designs may not be appropriate. Scientific justification for the alternative design used should be provided.

The need for long-term efficacy follow up should be considered.
Investigational Products in Korea

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Disease</th>
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<tbody>
<tr>
<td>Keratinocyte Chondrocyte</td>
<td>- Diabetic foot ulcer&lt;br&gt;- Burn wounds&lt;br&gt;- Cartilage defects</td>
</tr>
<tr>
<td>Dendritic cell Lymphocyte</td>
<td>- Cancer</td>
</tr>
<tr>
<td>BM MSC</td>
<td>- Acute cerebral infarction&lt;br&gt;- Acute myocardial infarction&lt;br&gt;- Graft vs. Host Disease&lt;br&gt;- Chronic spinal Injury&lt;br&gt;- Lou Gehrig’s disease</td>
</tr>
<tr>
<td>Cord blood MSC</td>
<td>- Cartilage injury&lt;br&gt;- Grafted HSC survival promotion&lt;br&gt;- Alzheimer’s disease</td>
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<tr>
<td>Adipose SC</td>
<td>- Burger’s disease&lt;br&gt;- Arthritis&lt;br&gt;- Crohn’s disease anal fistula&lt;br&gt;- Fecal incontinence&lt;br&gt;- Spinal injury</td>
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<tr>
<td>ESC-derived RPE</td>
<td>- Stargardt’s disease</td>
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* IND Approved; 60
* Under clinical trial; 40
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| Chondrocyte (auto) Keratinocyte (auto/allo) | - Articular cartilage defects  
|                                   | - Burn wounds  
|                                   | - Diabetic foot ulcer                        |
| Dendritic cell (auto) Activated lymphocyte (auto) | - Cancer                                    |
| Fibroblast (auto)                  | - Diabetic foot ulcer                        |
| Osteoblast (auto)                  | - Fracture  
|                                   | - Bone Necrosis                              |
| Adipocyte (auto)                   | - Treatment of scar                          |
Thanks