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

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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.**

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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

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<table>
<tr><th colspan="3"></th><th>Manufacturing</th><th>Autologous</th><th>Allogeneic</th><th>Xenogeneic</th></tr>
<tr><td rowspan="3">Cell</td><td rowspan="2">Minimal manipulation</td><td>at a medical center</td><td colspan="3" rowspan="2">Medical Practice
(Medical Service Act)</td></tr>
<tr><td>Outside the medical center</td></tr>
<tr><td colspan="2">More than minimal manipulation</td><td colspan="3" rowspan="2">Biologics
(Pharmaceutical Affairs Act)
: Cell therapy products</td></tr>
<tr><td colspan="3" rowspan="2">Tissue</td><td>Medical Practice
(Medical Service Act)</td><td>Human tissues for transplantation
(Human Tissue Safety & Control Act)</td><td>Medical Device
(some of products like porcine valve. Medical Device Act)</td></tr>
<tr><td colspan="3">Tissue-Engineered Products (Biologics or Medical Device)</td></tr>
<tr><td colspan="3">Organ</td><td>-</td><td>Human organs for transplantation
(Internal Organs, etc. Transplant Act)</td><td>-</td></tr>
</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

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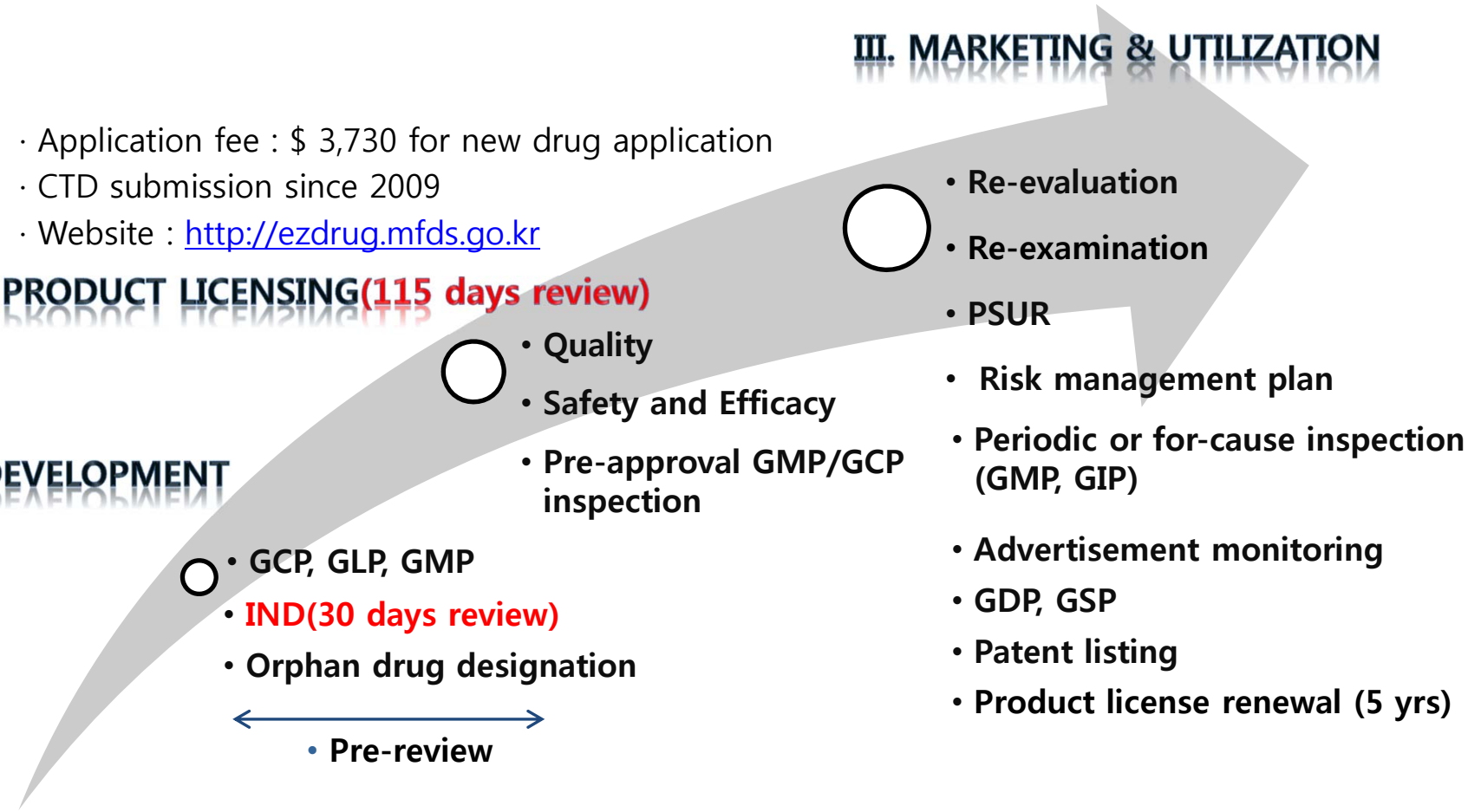

Regulatory Activities

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as of February 2016

▪ Currently Approved Cell Therapy Products

Products no.	Company no.	Cell & Manipulation				
		Stem cell	Immune cell	Somatic cell*	Minimal manipulation	Xenogeneic cell
14	10	4	2	7	1	0

▪ Approved Clinical Trials for Cell Therapy Products

No of	Clinical trials.	Sponsors	Cell type			
			Stem cell	Immune cell	Somatic cell*	Xenogeneic cell
SIT	116	30	63	29	23	1
IIT	88	29	48	32	8	0
Total	204	59	111	61	31	1

** keratinocytes, fibroblasts, chondrocytes , osteoblasts*

▪ Approved Clinical Trials for Gene Therapy Products

Clinical trials	Sponsors	Vector types					
		Plasmid	Adenovirus	Vaccinia	Gene modified cell	Plasmid+ Adenovirus	mRNA
43	20	18	9	7	6	1	2

14 Cell therapy products are authorized

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(as of February 2016)

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

Specific Consideration- Quality

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- **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

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- **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

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- **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

Regulatory Approach

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Offer Therapeutic Opportunities

- **Emergency IND**
- **Treatment IND**
- **Conditional Approval (NDA)**
  - anti-cancer drugs
  - orphan drugs
  - autologous keratinocytes and chodrocytes
- **Pre-review system (= Scientific advice)** → IND or NDA
  - CMC package
  - Pre-clinical and/or clinical data

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 (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~)

Majungmul(Priming water) Project

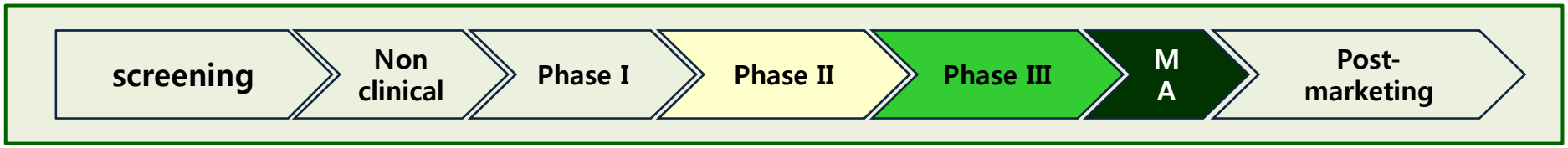
- Scientific advice program for facilitating innovative biological products

▪ addressing regulatory hurdles and difficulties for pursuing marketing authorization

03

Product based and tailored consultation for the product in late phase of development

: team consisting of regulatory experts



01

Educating researchers for basics in regulatory requirements

: biannual training program

02

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

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Thank you for your attention!