Regulatory Overview of Cell Therapy Products in Korea

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Sept. 11, 2015
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Disclaimer

- The followings represent the presenter's views based on my experience and not necessarily the views of the Korea Ministry of Food and Drug Safety.

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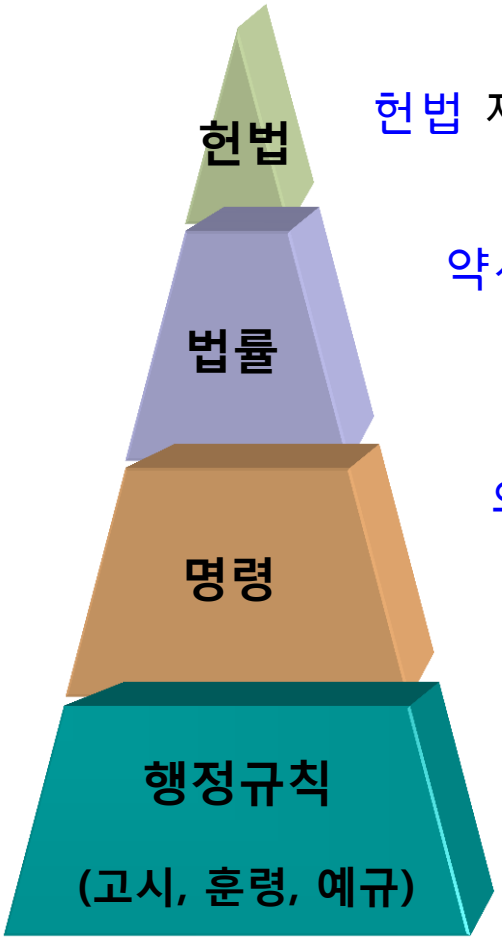
- Priming Water Project

의약품허가심사 관련 규정



헌법 제 36조: 국민은 보건에 관하여 국가의 보호를 받는다

약사법: 제조한 의약품을 판매 또는 수입하고자 하는 경우 품목별로 식약청 허가(신고)

의약품 등의 안전에 관한 규칙(총리령): 허가(신고) 대상, 기준, 조건, 관리 등 필요한 사항을 정함

식품의약품안전처 고시:
[생물학적제제 등의 품목허가,신고,심사 규정]
[의약품 임상시험 계획 승인에 관한 규정] 등

기타: 가이드라인, 지침(처리방안), 해설서 등
- 세포치료제 품질관리 시험항목 설정 가이드라인
- 학술연구목적 세포치료제 연구자임상시험 가이드라인 등

Cell therapy product is defined as

(식약처 고시: 생물학적제제 등의 품목허가심사 규정)

- 제2조(정의) "세포치료제"란 살아있는 자가, 동종, 이종세포를 체외에서 배양 증식하거나 선별하는 등 물리적, 화학적, 생물학적 방법으로 조작하여 제조하는 의약품을 말한다.
  다만, 의료기관내에서 의사가 자가 또는 동종세포를 당해 수술이나 처치과정에서 안전성 등에 문제가 없는 최소한의 조작(생물학적 특성이 유지되는 범위 내에서의 단순한 분리, 세척, 냉동, 해동 등)만을 하는 경우는 제외한다.

Regulation of Cell & Tissue based Products

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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><td rowspan="3"></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 under HTSCA : cartilage, bone, ligament, tendon, skin, heart valves, blood vessel, fascia, amnion***

Cell Therapy Products in Korea (1)

(June, 2015)

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▪ Currently Approved Products

Products no.	Company no.	Cell & Manipulation				
		Stem cell	Immune cell	Somatic cell*	Minimal manipulation	Xenogeneic cell
13	10	4	2	6	1	0

▪ Approved Clinical Trials

	Clinical trial no.	Company no. Hospital no.	Cell type			
			Stem cell	Immune cell	Somatic cell*	Xenogeneic cell
SIT	103	28	53	27	22	1
IIT	83	27	46	29	8	0
Total	186	55	99	56	30	1

** keratinocytes, fibroblasts, chondrocytes , osteoblasts*

Stem Cell Products in Korea (June, 2015)

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◆ NDA approved (4)

- Bone marrow-derived MSC(auto): Improvement of left ventricular ejection fraction(AMI)
- Umbilical cord blood-derived MSC(allo): Articular cartilage defects (Knee)
- Adipose-derived MSC(auto): Complex peri-anal fistula (Crohn's disease)
- Bone marrow-derived MSC(auto): Amyotrophic Lateral Sclerosis

◆ IND approved (99)

Cell Source	Portion (%)
Adipose	35
Bone Marrow	30
Cord Blood, Placenta	24
Embryonic	5
Others	5

Therapeutic area	Portion (%)
Neurological disorders	22
Cardiovascular	19
Joint disorders	13
Peri-anal fistula	11
Immune-related	11
Eye disease	6
Others	18

Approved Stem Cell Products (1) (June, 2015)

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[HEARTICELLGRAM-*AMI* ®]

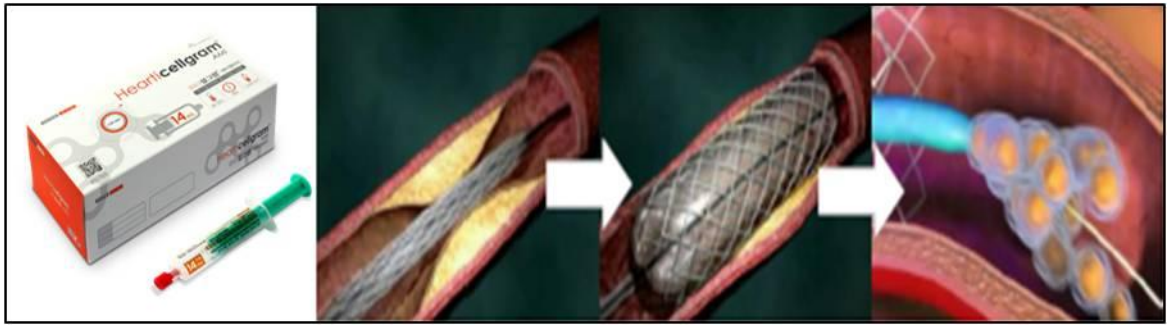
- Jul. 2011 approved

- Composition : Autologous bone marrow-derived mesenchymal stem cell

- Indication : Acute myocardial Infarction

- Approval condition
  - Long-term F/U of patients enrolled in clinical trials
  - Clinical trial for long-term safety & efficacy
  - Re-examination
  - Safety follow-up for all the treated patients after MA

- Direction and dose



Intracoronary Artery Infusion using a catheter

- **No more than 60kg : 10㎖ / 5 X 10^7 cells**
- **61kg ~ 80kg : 14㎖ / 7 X 10^7 cells**
- **Not less than 81kg : 18㎖ / 9 X 10^7 cells**

Approved Stem Cell Products (2) (June, 2015)

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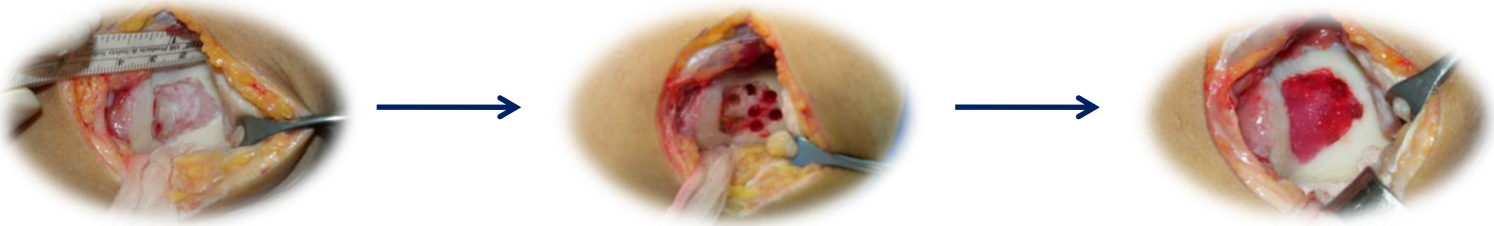
[CARTISTEM®]

- Jan. 2012 approved
- Composition : allogeneic umbilical cord blood-derived mesenchymal stem cell
- Indication : Knee articular cartilage defects
  Treatment of knee articular cartilage defects in patients with osteoarthritis (ICRS grade IV) as a result of degenerative disease or repeated trauma
- Approval condition
  - Long-term F/U of patients enrolled in clinical trials
  - Re-examination
  - Safety follow-up for all the treated patients after MA
- Directions and dose



Exposing the cartilage defect via arthrotomy

Create multiple holes

Fill in the holes with Cartistem

Approved Stem Cell Products (3) (June, 2015)

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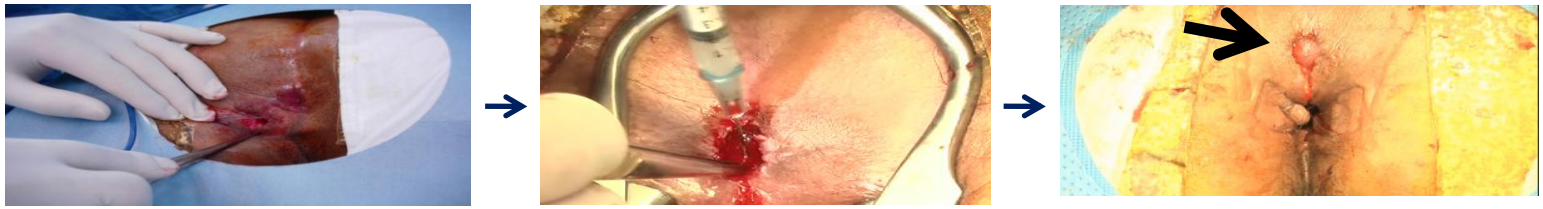
[CUPISTEM®]

- Oct. 2008 orphan drug designation
- Jan. 2012 approved as orphan drug
- Composition : autologous adipose-derived mesenchymal stem cell
- Indication : Treatment of Crohn's fistula
- Approval condition
  - Long-term F/U of patients enrolled in clinical trials
  - Phase 3 clinical trial for long-term safety & efficacy
  - Safety follow-up for all the treated patients after MA
- Directions and dose



Curettage → Inject Cupistem → Fill with fibrin glue

Approved Stem Cell Products (4) (June, 2015)

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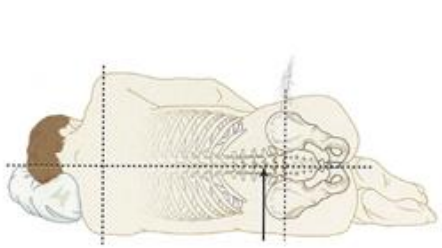
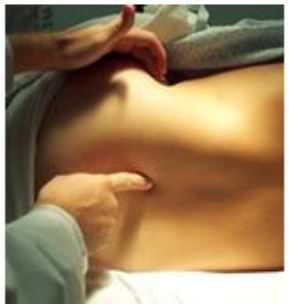
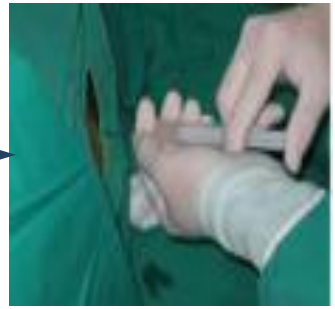
[NEURONATA-R® Injection]

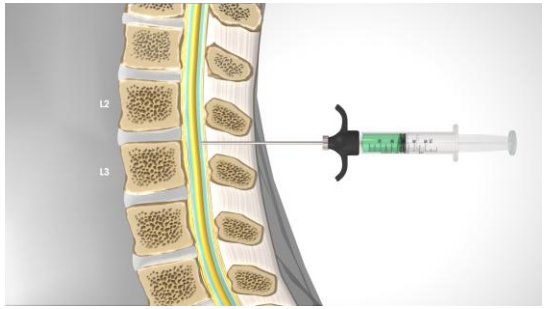
- Dec. 2013 orphan drug designation
- Jul. 2014 approved as an orphan drug
- Composition: autologous bone-marrow derived mesenchymal stem cells
- Indication: ALS treatment by delaying disease progression in combination with riluzole
- Approval condition
  - Long-term F/U of patients enrolled in clinical trials
  - Phase 3 clinical trial to evaluate safety and efficacy
  - Implementation of risk management plan(RMP) including long term follow-up for all the treated patients
- Direction and dose: intrathecal injection by 0.1mL per patient's body weight(kg)





Lumbar puncture





Intrathecal injection

MFDS Organization : HQ, NIFDS, 6 RO

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Korea MFDS(As of April, 2015)

- 1 headquarter, 6 regional offices,
  1 affiliated institute(NIFDS),
  13 imported food inspection centers
- Total number of employees : 1,763
- Budget : $ 395 millions (including R&D)

Headquarter

7 Bureaus, 1 office, 45 Divisions

- Minister
  - Vice Minister
    - Director General for Planning and coordination — 7 Divisions
    - Customer Risk Prevention Bureau — 4 Divisions
    - Food Safety Policy Bureau — 6 Divisions
    - Food Nutrition and Dietary Safety Bureau — 4 Divisions
    - Agro-Livestock and Fishery Products Safety Bureau — 4 Divisions
    - Pharmaceutical Safety Bureau — 7 Divisions
    - Biopharmaceuticals and Herbal Medicine Bureau — 5 Divisions
    - Medical Device Safety Bureau — 3 Divisions

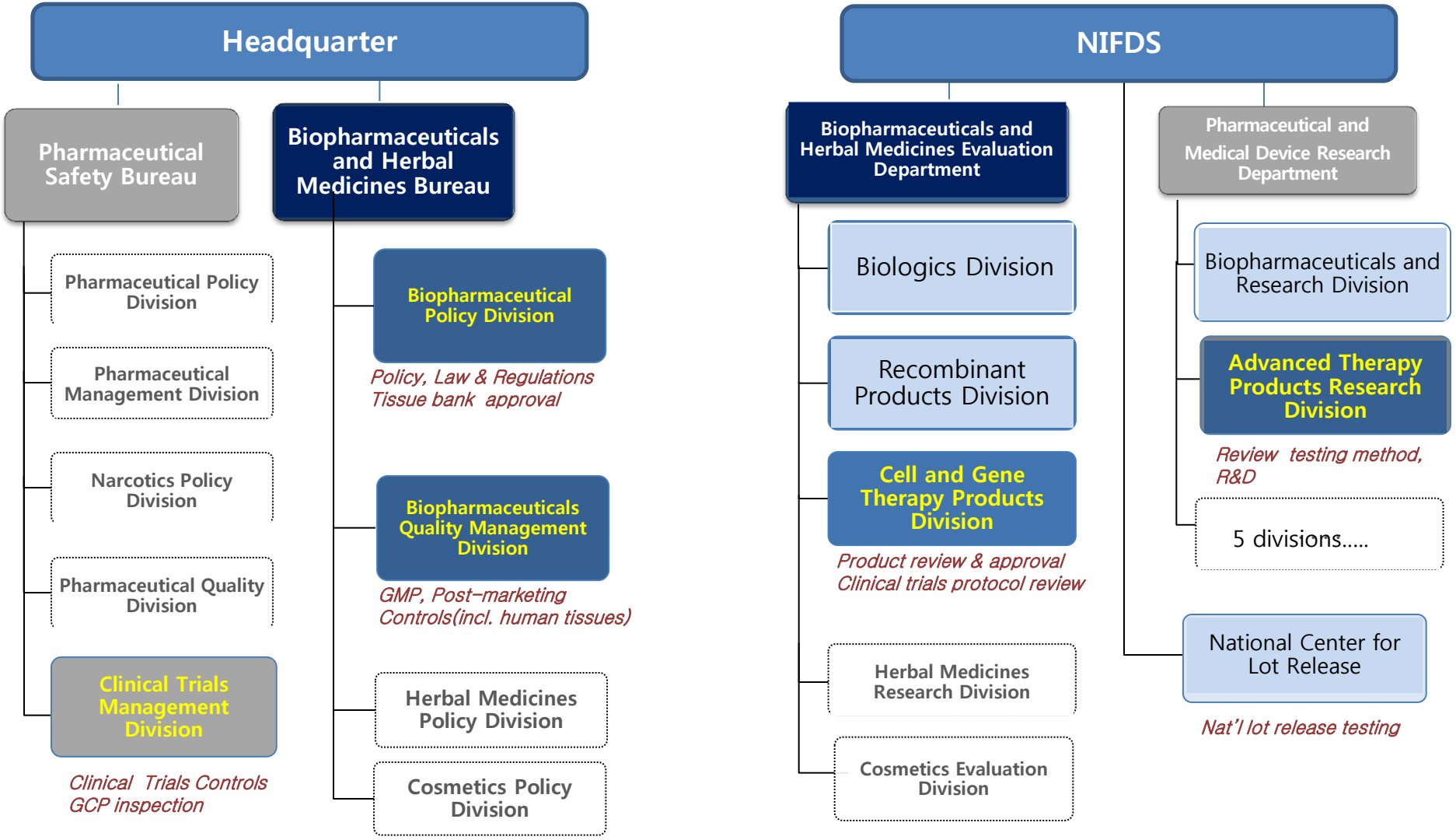
NIFDS

6 Departments, 39 Divisions

- Director General
  - Research Planning & Management Division
  - Vaccines Division
  - Blood Products Division
  - Food Safety Evaluation Department — 9 Divisions
  - Drug Evaluation Department — 6 Divisions
  - Biopharmaceuticals and Herbal Medicine Evaluation Department — 5 Divisions
  - Medical Device Evaluation Department — 5 Divisions
  - Pharmaceutical and Medical Device Research Department — 6 Divisions
  - Toxicological Evaluation and Research Department — 6 Divisions

6 Regional Offices

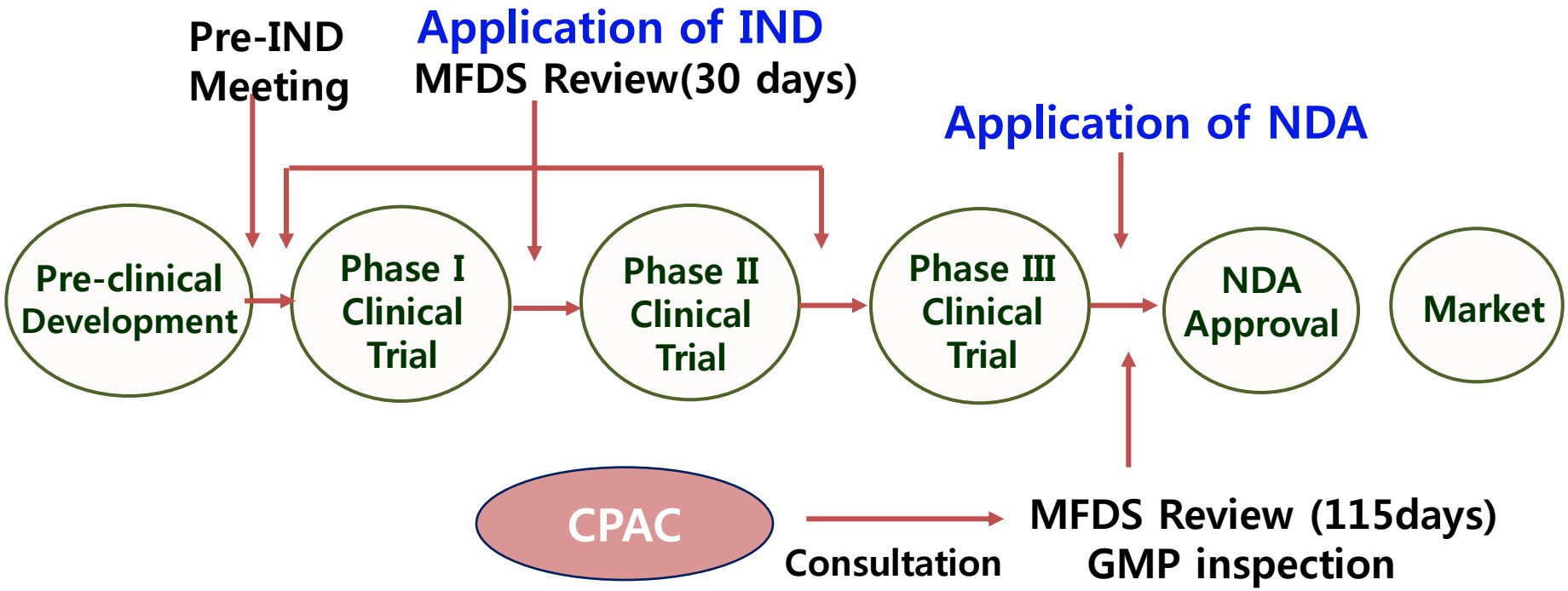
Offices Responsible for Biologics



IND & NDA Process for Biological Products

GLP GCP GMP

Re-examination
Re-evaluation
PSUR reporting
Product license renewal
Periodic GMP inspection
Advertisement monitoring



*CPAC : Central Pharmaceutical Affairs Advisory Committee

Regulatory Requirements for IND

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Enforcement Rule of Medicinal Products Safety, article 24

- ✓ Clinical protocol
- ✓ GMP documents
- ✓ Specifications and Test Methods
- ✓ Safety and Efficacy materials according to MFDS notification

Regulation on Approval of IND for Medicinal Products (MFDS Notification)
(article 4: Safety and Efficacy materials)

- ✓ General investigational plan
- ✓ Introductory statement
- ✓ Physico-chemical and biological characterization of product
- ✓ Pre-clinical data
- ✓ Previous clinical experience
- ✓ Investigator's brochure

Regulatory Requirements for NDA

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Enforcement Rule of Medicinal Products Safety, article 4

- ✓ Safety and Efficacy Materials (pre-clinical, clinical)
- ✓ Specification & Test Methods (chemistry, manufacturing and control Information
- ✓ GMP Documents
- ✓ Manufacturer's Information
- ✓ Certificate of Pharmaceutical Product-imported product
- ✓ Certificate of Patent Confirmation

Regulation on Review and Authorization of Biological Products (MFDS Notification)

Section 1 : General
Section 2 : NDA application
Section 3 : Safety and Efficacy Evaluation
Section 4 : Quality Evaluation

Specific Considerations: General

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- ✓ Great Potential for Unmet Medical Needs
- ✓ Emerging Innovative Field
- ✓ Limited Clinical Experience
- ✓ Considerable Uncertainty
  - complexities and dynamic reactions affected by microenvironment
  - lack of completing understanding of cellular characteristics
- ✓ Prolonged Biological Activity
  - unknown long-term risks
  - requires long-term follow-up of patients
- ✓ Not fully characterized mechanism of action
- ✓ Customized preparation of products

Specific Considerations: Quality

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✓ **Maintenance of aseptic condition**

- final products are living cells, limit in microbiological free condition
- 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

  => 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 from phenotype, genotype, synthesis of bio-active factors, etc

Specific Considerations: Pre-clinical

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✓ **Species specificity and immunogenicity in xeno-transplantation**

✓ **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, immunodeficient animals
- study design? appropriate positive and negative control ?

Specific Considerations: 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 pre-clinical 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

  => standardized procedure & delivery design, 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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The Risk-Based, Case-by-Case Approach

Scientific Evidence-Based Review with Flexibility

Balancing Risk and Benefit

Offer Therapeutic Opportunities

- Emergency IND
- Treatment IND
- Conditional Approval
  - anti-cancer drugs
  - orphan drugs
  - autologous Keratino. & Chondro
- Pre-review system

Ensure Safety of the Patients

- Re - examination of new drug
  - examine any adverse events not in CT
  - new drugs: 6 years, 3000 patients
  - other drugs: 4 years, 600 patients
  - data exclusivity
- Re - evaluation of drug
  - periodically re-evaluate labels
  - -> license renewal in five-year intervals
- Mandatory safety reporting for every use of approved cell therapy products

“Priming Water Project” for GT & CT Products

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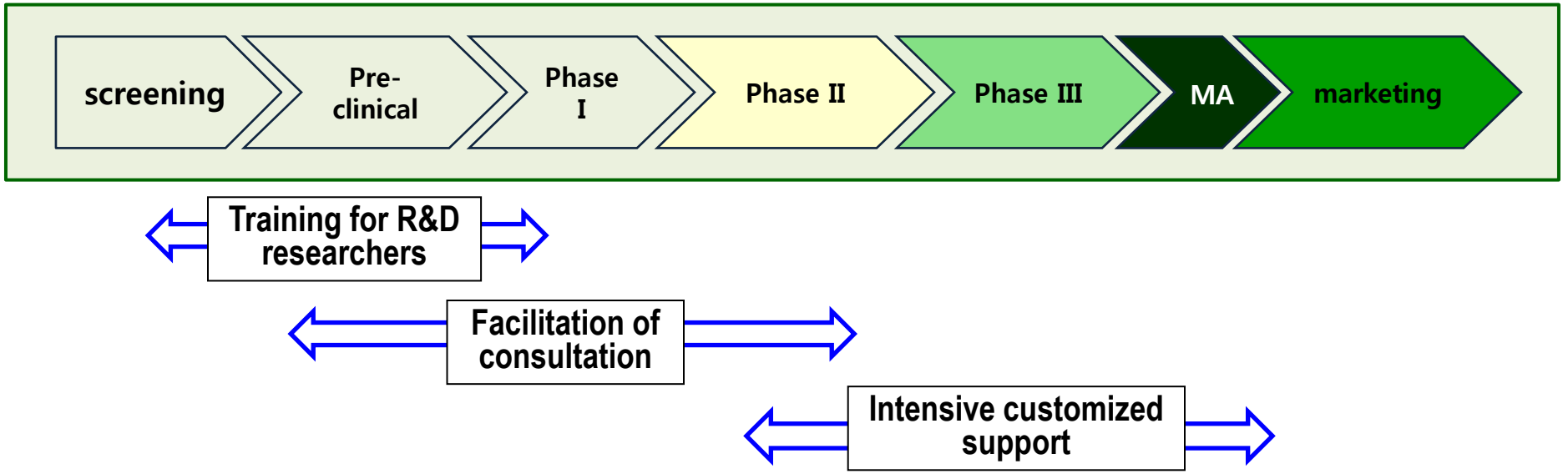
(MFDS homepage)

1. Education program for R&D researchers : basic regulatory requirements
   - bi-annual workshop (Sept. & Feb)
2. Expanding consultation opportunities at the early stage of product development
   - every Wednesday of last week of the month
3. Intensive and customized support to products close to commercialization stage
   - team consultation
4. Establishment of pre-clinical ‘Biodistribution Study’ lab



MFDS Guidelines for Biological Products

(http://mfds.go.kr/index.do?mid=689)

- Considerations for Evaluation of Dendritic Cell Therapy Products for Cancer Treatment (2005)
- Guideline on Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Application (2005)
- Guideline on Mycoplasma Test Suitable for Cell Therapy Products (2008)
- Considerations for Validation of Quantitative Polymerase Chain Reaction Method for Bio-distribution Test of Gene Therapy Products (2010)
- 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)
- The others

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Thank you

감사합니다