Korean Perspective on Biologics Regulation

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Korea Food and Drug Administration

2008. 1. 17.
Milestones

1945  National Chemistry Laboratory (NCL)
1959  National Institute of Health (NIH)
1987  National Institute of Safety Research (NISR)
1996  Korea Food and Drug Safety Headquarter and Six Regional Offices
      Reorganization of NISR to
      National Institute of Toxicological Research
1998  Korea Food and Drug Administration
2002  Reorganization of NITR
Mission & Vision of KFDA

Introduction | KFDA News | Major Policy | NITR | FAQ | Related Site

KOREA FOOD & DRUG ADMINISTRATION

The government agency committed to protecting consumers and promoting the public health

VISION

Promoting the public health by ensuring the safety and efficacy of foods, pharmaceuticals, medical devices and cosmetics, and supporting the development of the food and pharmaceutical industries

Building a reliable foundation for manufacture and supply of safe foods and pharmaceuticals

Strengthening law enforcement against manufacturers of defective law quality foods and pharmaceuticals

Establishing a system designed to support the food and pharmaceutical industries

Promoting private sector participation and improving public services
Biologics Headquarters

◆ Biologics Safety Policy & Management (2 Teams)
  - Coordinates administrative work: IND, NDA, PMS, GMP inspection
  - Coordinates all compliance actions: product recalls, regulatory letters
  - Final decision for approval and issue approval certificate

◆ Biologics Evaluation (7 Teams)
  - Evaluates CMC section
  - Evaluates pharmacology, toxicology and clinical data section
  - Supports GMP, GLP, GCP compliances
  - Performs official lot release tests of biologics
  - Conducts laboratory research

◆ Central Pharmaceutical Affairs Council
  - Advisory Committee

◆ Clinical management team and Biostatistics team support the clinical study and analysis of clinical statistics
**Biologics Regulated by KFDA**

- **Vaccines**
  - These products are administered to millions of healthy people including infants

- **Blood products**
  - Blood components, plasma derived product (clotting factors, etc.)

- **Therapeutic proteins**
  - Recombinant products (growth hormones, EPO, cytokines, etc.), mAb products

- **Cell therapy products**
  - Autologous, allogeneic, xenogeneic
  - Mesenchymal stem cell, cord blood stem cell, dendritic cell.

- **Gene therapy products**

- **In vitro diagnostics**
  - Test kits used to screen donor blood and to diagnose, treat, monitor persons with disease (HIV, hepatitis, etc.)
  - BioChip
Unique Challenges for Biologics

- Must be processed under defined conditions throughout production to consistently produce a safe, pure and potent product and preclude the introduction of environmental contamination.

- Cannot withstand heat sterilization—must be aseptically processed.

- Stability is an issue—product may need frozen storage or preservatives. Shelf life may be limited.
Documentation submitted to KFDA in order to start clinical studies

Type of INDs

- Commercial IND: Marketing approval
- Non-commercial IND:
  - An Investigator IND: clinical trial initiated by an investigator without any sponsor’s request in order to study an unapproved drug. A physician might submit a research IND
  - Emergency Use IND: to use an investigational drug in case of emergency before IND being approved
  - Treatment IND: to use an investigational drug or unapproved drug in order to treat a serious or life-threatening conditions
Scope of Dossier for IND

- Investigation Plan
- Introduction
- Chemistry, Manufacturing and Controls
- non-clinical data
- Clinical Result (if possible)
- Clinical Protocol
- Investigator Brochure
Scope of Dossier for NDA

- Introduction
  - Development background, purpose, history etc.
- Chemistry, Manufacturing and Controls
  - Validation data, raw data
- Stability Data
- non-clinical Test
  - Toxicology data
  - Pharmacology data
- Clinical Data
  - Clinical Trial Data Package
  - Bridging data
- Foreign registration status
Types of Inspections:

- **Pre-approval inspection**
  : to verify the completeness and accuracy of information submitted to the KFDA in support of NDA

- **Routine GMP inspection**
  : Surveillance inspection for GMP compliance

- **For cause inspection**
  : conducted because of an issue such as recalls, field alerts or adverse reactions

**Regional KFDA participates the GMP inspection**
◆ KFDA inspects sponsor/monitor and clinical sites:
  - To verify the integrity of efficacy and safety data submitted to the KFDA in support of NDA
  - To assure that the rights and welfare of human research subjects are protected

◆ Site selection:
  - Investigators who conducted pivotal studies
  - Investigators with high enrollment or conducted multiple studies with product
Diagram of Review Process

1. Pre IND meeting
   Application

2. Consultation

3. Notification
   IND Application (amendment)

4. IND approval

5. IND package
   Protocol, IB

6. Clinical Trial
   ongoing

7. Reporting of CT
   completion

8. NDA Application

9. NDA requisite
   Dossier

10. Final product
    Approval

- 50 days
- 30 days
- 145 days
Post-marketing Surveillance

◆ Collection of safety information:
  - from drug manufacturers, healthcare providers, medical journals and WHO international drug monitoring program
  - Manufacturers and healthcare providers are required to report the death or disablement, in-hospital treatment or other serious adverse reaction
  - Voluntary for consumers and physicians
  - Mandatory for manufacturers, distributors within 15 days

◆ Actions
  - Based on review results, KFDA may change indications, warnings and precautions for use
  - Supply information to healthcare providers by ‘Dear Healthcare Professional/Pharmacist Letter’
In case of vaccine, Korea CDC controls the reporting system under ‘Infectious Disease Prevention Act’

- **1994**: introduce *Monitoring System for AEFI (Adverse Events Following Immunization)*
  - Cases of death after JE vaccination were reported in 1994

- **1995**: introduce *National Vaccine Injury Compensation Program*

- **2000**: Doctors are required by legislation to report AEFI

- **2002**: introduce *National Immunization Registries System*
Re-examination system

- Data submitted for approval is not always adequate
- System was established in order to re-examine the efficacy and safety of new drug for some period after approval

- **6 years:**
  - New drugs
  - Drugs including new active ingredients
  - Drugs have same active ingredients but different route of administration

- **4 years:**
  - Drugs have same active ingredients and route of administration but different indications
Re-evaluation system

- The safety and efficacy of approved drugs are re-evaluated by recent scientific evidence
- Manufacturer have to demonstrate their product has same efficacy and safety specified in approval certificate

**Results of re-evaluation**

- Manufacturer may produce the approved drug if the drug are shown the safety and efficacy
- Manufacturer has to change insert, label if necessary
- KFDA withdraw the approval and manufacturer have to withdraw the product on the market when they can not show their safety and efficacy
Clinical Trial in Korea

◆ Milestones of Korea GCP

1987   Establishment of KGCP (recommendation)
1995   Requirement for compliance of KGCP
1999   Adoption of the Bridging Concept
2001   Harmonized with ICH GCP guideline
        Establishment of Pharmaceutical Act Article 26-4
        (’07. 4.11 changed to Article 34)
        - require to approval of clinical trial from KFDA
        - prohibition for selecting “vulnerable subjects”
        - protect the rights and safety of subjects

2002   Introduction of IND
        - Separation between developmental clinical stage and commercial product approval, IND and NDA
Clinical Trial Approval Process

**KFDA Process**
- Pre-IND meeting
- Submission → Review → Approval
  - CMC
  - Pre-clinical
  - Protocol
  - IB

**IRB Process**
- Parallel review with KFDA process
- Submission → Review → Approval
  - CV
  - Protocol
  - IB
  - CRF

Timeline: 30 days

Contract with Hospital
Clinical Trials Approved in KFDA

Drug | Biologics
---|---
'03 | 143 | 34
'04 | 136 | 14
'05 | 185 | 34
'06 | 218 | 27
'07 | 280 | 41
Clinical Trials Approved of Biologics (’03-’07)

- Therapeutics: 84
- Cell Therapy: 27
- Gene Therapy: 8
- Vaccines: 25
- Others: 6
### Clinical Trials in Korea

**http://ezdrug.kfda.go.kr**

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
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<tbody>
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<td>신청자</td>
<td>제품명</td>
<td>성분명</td>
<td>승인일</td>
<td>서울대학교병원</td>
<td>실험체 목</td>
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<td>에스케이케미칼</td>
<td>염산날루라핀</td>
<td>염산날루라핀</td>
<td>2008-01-02</td>
<td>서울대학교병원</td>
<td>혈액투석환자 중 기존요양증 치료에 저항성을 나타내는 환자에서 TRK-820의 유호성 및 안전성을 평가하기 위한 이중논가립. 무작위배정, 위약대조, 병렬. 대기 관제3상 임상시험</td>
</tr>
<tr>
<td>3</td>
<td>한국화이자제약</td>
<td>인스프라</td>
<td>에플리레노</td>
<td>2008-01-02</td>
<td>삼성서울병원. 연세대세브란스병원. 아주대학교병원</td>
<td>NYHA CLASS II의 만성 수축기 심부전 환자에서 심혈관 사망 및 심부전 입원에 대한 EPLERENONE의 위약 효과</td>
</tr>
<tr>
<td>4</td>
<td>동아제약</td>
<td>DA-8159</td>
<td>DA-8159</td>
<td>2008-01-02</td>
<td>서울대학교병원</td>
<td>간장이 환자와 간해가 자원자에서 udenafil의 약물학적 특성을 평가하기 위한 임상시험</td>
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<tr>
<td>5</td>
<td>한국베리링거인제합업</td>
<td>BIBR 1048 MS캡슐 110, 150mg</td>
<td>Dabigatran Exetilate</td>
<td>2008-01-03</td>
<td>다정</td>
<td>급성 종후성 정맥 혈전색전증에 대해 승인된 비경구적 항응고제로 초기에 6일 이상 치료한 후 6개월 동안 투여된 경구용 dabigatran etexilate (150 mg 1일 2회)의 유호성 및 안전성을 와파린 (INR 2.0~3.0)과 비교하여 평가하기 위한 제3상 무작위배정. 이중맹검. 평행군 임상시험</td>
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</tbody>
</table>
Cell therapies are products composed of human or animal cells or from physical parts of those cells.


Manufacturing process carried out in dedicated facilities complying with GMP.

More than minimal manipulation - *ex vivo* proliferation, pharmacological treatment of cells, other alteration of their biological characteristics.
## Cell Therapy Products Approved in Korea

<table>
<thead>
<tr>
<th>Product</th>
<th>Cell Type</th>
<th>Indication</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondron</td>
<td>Chondrocyte (auto)</td>
<td>Articular cartilage defects</td>
<td>NDA-approved ('01)</td>
</tr>
<tr>
<td>Articel</td>
<td>Chondrocyte (auto)</td>
<td>Articular cartilage defects</td>
<td>NDA-approved ('02)</td>
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<tr>
<td>Holoderm</td>
<td>Keratinocyte (auto)</td>
<td>Burn wounds</td>
<td>NDA-approved ('02)</td>
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<tr>
<td>Kaloderm</td>
<td>Keratinocyte (allo)</td>
<td>Burn wounds</td>
<td>NDA-approved ('05)</td>
</tr>
<tr>
<td>Adipocel</td>
<td>Adipocyte (auto)</td>
<td>Treatment of scar</td>
<td>NDA-approved ('07)</td>
</tr>
<tr>
<td>Product</td>
<td>Cell Type</td>
<td>Indication</td>
<td>Status</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------</td>
<td>---------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Hyalograft 3D</td>
<td>Fibroblast (auto)</td>
<td>Diabetic Foot Ulcer</td>
<td>MA (Phase 3)</td>
</tr>
<tr>
<td>Autocel</td>
<td>Keratinocyte (auto)</td>
<td>Burn wounds</td>
<td>MA (Phase 3)</td>
</tr>
<tr>
<td>Inno-LAK</td>
<td>Activated Lymphocyte (auto)</td>
<td>Lung Cancer</td>
<td>MA (Phase 3)</td>
</tr>
<tr>
<td>Immunecell-LC</td>
<td>Activated Lymphocyte (auto)</td>
<td>Liver Cancer</td>
<td>MA (Phase 3)</td>
</tr>
<tr>
<td>Cravat-RCC</td>
<td>Dendritic cell (auto)</td>
<td>Kidney Cancer</td>
<td>MA (Phase 3)</td>
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<tr>
<td>NKM</td>
<td>Activated lymphocyte (auto)</td>
<td>Lymphoma</td>
<td>MA (Phase 3)</td>
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</tbody>
</table>

* M.A. : Marketing Approval
<table>
<thead>
<tr>
<th>Product</th>
<th>Cell Type</th>
<th>Indication</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ostem</td>
<td>Osteoblast (auto)</td>
<td>Fracture</td>
<td>Phase 3</td>
</tr>
<tr>
<td>DCVac-EPL</td>
<td>Dendritic cell (auto)</td>
<td>Lung Cancer</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td>DCVac-IR</td>
<td>Dendritic cell (auto)</td>
<td>Colon Cancer</td>
<td>Phase 1/2a</td>
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<tr>
<td>Creavax-PC</td>
<td>Dendritic cell (auto)</td>
<td>Prostate Cancer</td>
<td>Phase 1/2a</td>
</tr>
<tr>
<td>MSC1</td>
<td>BM MSC (auto)</td>
<td>Acute cerebral infarction</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>
## Cell Therapy Products under Clinical Trial

<table>
<thead>
<tr>
<th>Product</th>
<th>Cell Type</th>
<th>Indication</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartistem</td>
<td>Cord blood MSC (allo)</td>
<td>Chronic cartilage defects</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td>DCVac-EPB</td>
<td>Dendritic cell (auto)</td>
<td>Mammary Cancer</td>
<td>Phase 1/2a</td>
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<tr>
<td>TK Cell</td>
<td>Activated Lymphocyte (auto)</td>
<td>Gastric Cancer Colon Cancer</td>
<td>Phase 2</td>
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<tr>
<td>Myocell</td>
<td>Myoblast (auto)</td>
<td>Congestive Heart Failure</td>
<td>Phase 2</td>
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<td>Kaloderm</td>
<td>Keratinocyte (auto)</td>
<td>Diabetic Foot Ulcer</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Product</td>
<td>Cell Type</td>
<td>Indication</td>
<td>Status</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------</td>
<td>--------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Inno LC-01</td>
<td>Activated Lymphocyte (auto)</td>
<td>Brain Cancer</td>
<td>Phase 3</td>
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<tr>
<td>Cerecellgram-spine</td>
<td>BM MSC (auto)</td>
<td>Chronic Spinal Cord Injury</td>
<td>Phase 2/3</td>
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<tr>
<td>MSC2</td>
<td>BM MSC (auto)</td>
<td>Myocardial infarction</td>
<td>Phase 2/3</td>
</tr>
<tr>
<td>Vascostem</td>
<td>Adipose tissue cell</td>
<td>Buerger’s Disease</td>
<td>Phase 1/2</td>
</tr>
</tbody>
</table>
Regulation of Cell & Tissue

- Regulated by ‘Human Tissue Safety & Control Act’ from 2004
- Intended to prevent introduction, transmission and spread of communicable diseases by
  - Preventing use of human cell/ tissue from ineligible donors
  - Preventing improper handling or processing that might contaminate cell/tissue
    - Cartilage, Bone, Ligament, Tendon, Skin
    - Human heart valves, Blood Vessel
- KFDA does not regulate the transplantation of human organ transplants such as kidney, liver, heart, lung or pancreas
- ~100 tissue banks approved by KFDA
Gene therapies introduce genetic material into the human body to replace a defective or missing gene or to treat or cure disease.


- There is no approved gene therapy product in Korea.

- 8 products under clinical trial.
## Gene Therapy Products under Clinical Trial

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Status</th>
<th>Vector (gene)</th>
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<tbody>
<tr>
<td>VMDA3601</td>
<td>Ischemic Foot Ulceration</td>
<td>II</td>
<td>Plasmid DNA (VEGF)</td>
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<tr>
<td>GX-12</td>
<td>HIV Infection</td>
<td>I</td>
<td>Plasmid DNA (Ag &amp; IL-12)</td>
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<td>JX-594</td>
<td>Liver Cancer</td>
<td>I</td>
<td>Vaccinia virus (TK &amp; CSF)</td>
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<td>VM206RY</td>
<td>Ischemic Heart Disease</td>
<td>I</td>
<td>Plasmid DNA (HGF)</td>
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<td>TissueGene-C</td>
<td>Osteoarthritis</td>
<td>I</td>
<td>Retrovirus (TGF-β)</td>
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<td>VM106</td>
<td>Chronic Granulomatus Disease</td>
<td>I/IIa</td>
<td>Retrovirus (gp91)</td>
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<td>Theragene</td>
<td>Prostate Cancer</td>
<td>II</td>
<td>Adenovirus (TK &amp; CD)</td>
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<td>HB-110</td>
<td>Chronic Hepatitis B</td>
<td>I</td>
<td>Plasmid DNA (Ag &amp; IL-12)</td>
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<tr>
<td>Product</td>
<td>Indication</td>
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<tr>
<td>-------------------------------------</td>
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<tr>
<td>HPV DNA chip</td>
<td>Diagnosis for HPV</td>
<td>Biomedlab</td>
<td>‘04</td>
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<td>MyHPV</td>
<td>Diagnosis for HPV</td>
<td>Mygene</td>
<td>‘04</td>
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<td>Macrogen BAC Chip H 1440</td>
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<td>‘06</td>
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<td>Goodgene HPV DNA Genotyping Chip</td>
<td>Diagnosis for HPV</td>
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<td>‘07</td>
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<td>HPV Genotyping chip</td>
<td>Diagnosis for HPV</td>
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<td>‘07</td>
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</table>
Future Challenges

◆ Rolling submission
  - Sponsor may submit CMC, non-clinical data and clinical data, separately

◆ Introduction of CTD
  - Mandatory for new biologics from 2009

◆ Introduction of investigational GMP
  - GMP guideline of product for clinical trial

◆ Introduction of institutional GMP
  - GMP guideline for gene/cell therapy products
Thank you!

Please send questions or comments to:

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- E-Mail: shhon8@kfda.go.kr
- Tel: 02-380-1711
- Fax: 02-386-6584