Korean Perspective on Biologics Regulation

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Korea Food and Drug Administration

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

식의약품 종합정보서비스 KIFDA

주소(D) http://www.kfda.go.kr/

KFDA KOREA FOOD & DRUG ADMINISTRATION

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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

KFDA NEWS

DETAIL VIEW

RELEVANT RULE

DETAIL VIEW

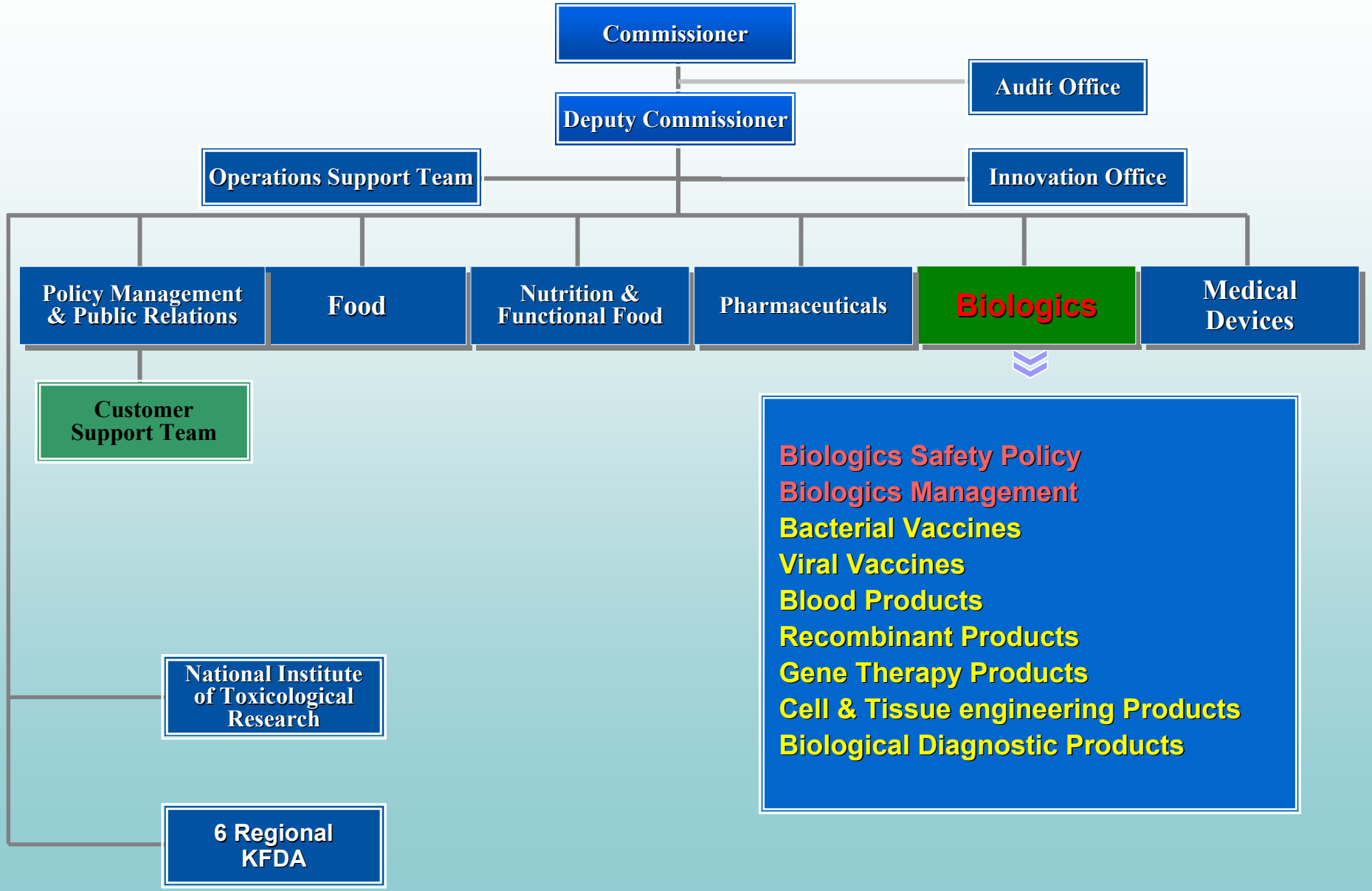
01 Building a reliable foundation for manufacture and supply of safe foods and pharmaceuticals

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

03 Establishing a system designed to support the food and pharmaceutical industries

04 Promoting private sector participation and improving public services

Organization Chart



Biologics Headquarters

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- **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 srem 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

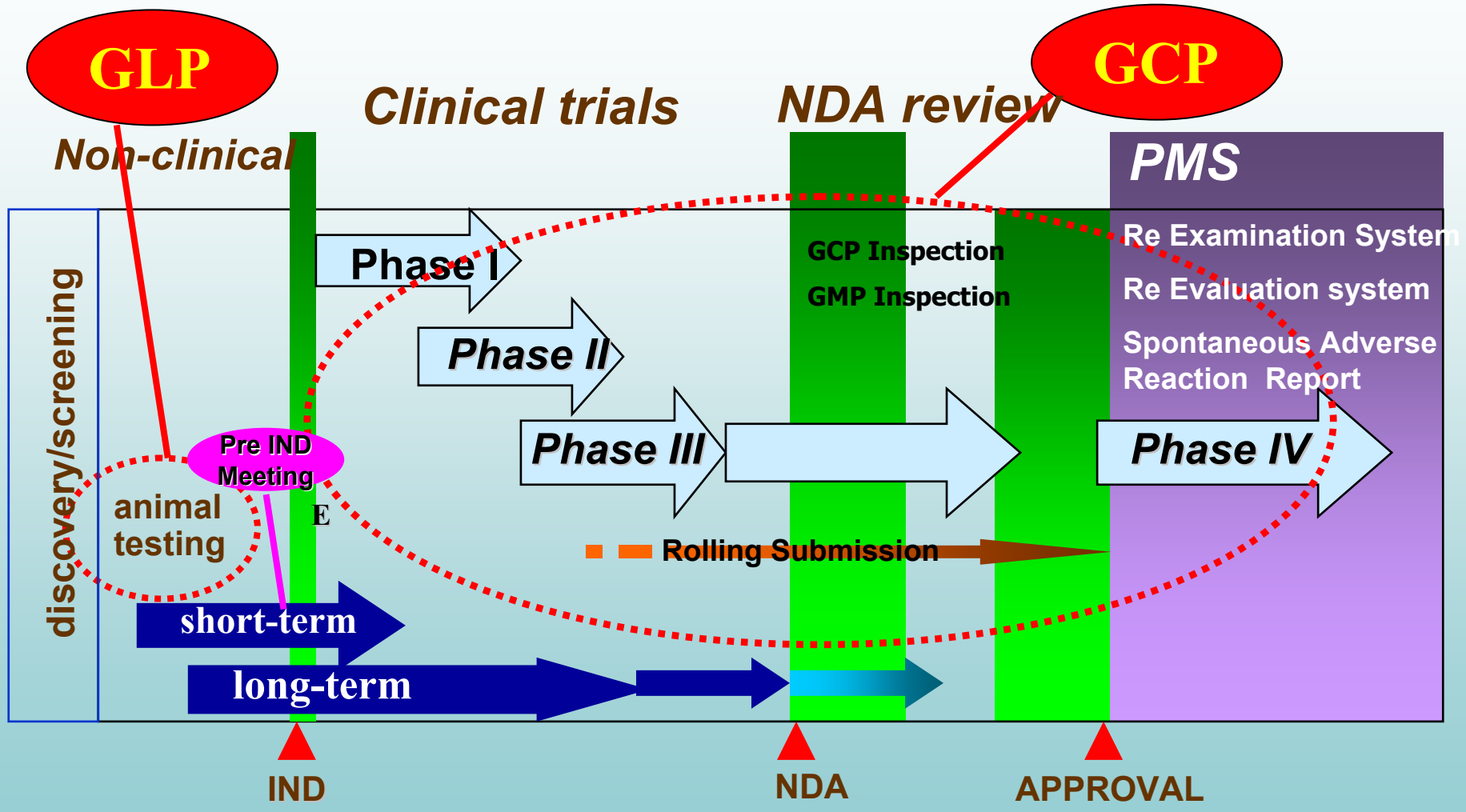
Unique Challenges for Biologics

- 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

Approval Pathway



IND

- 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**

GMP Inspection

- **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**

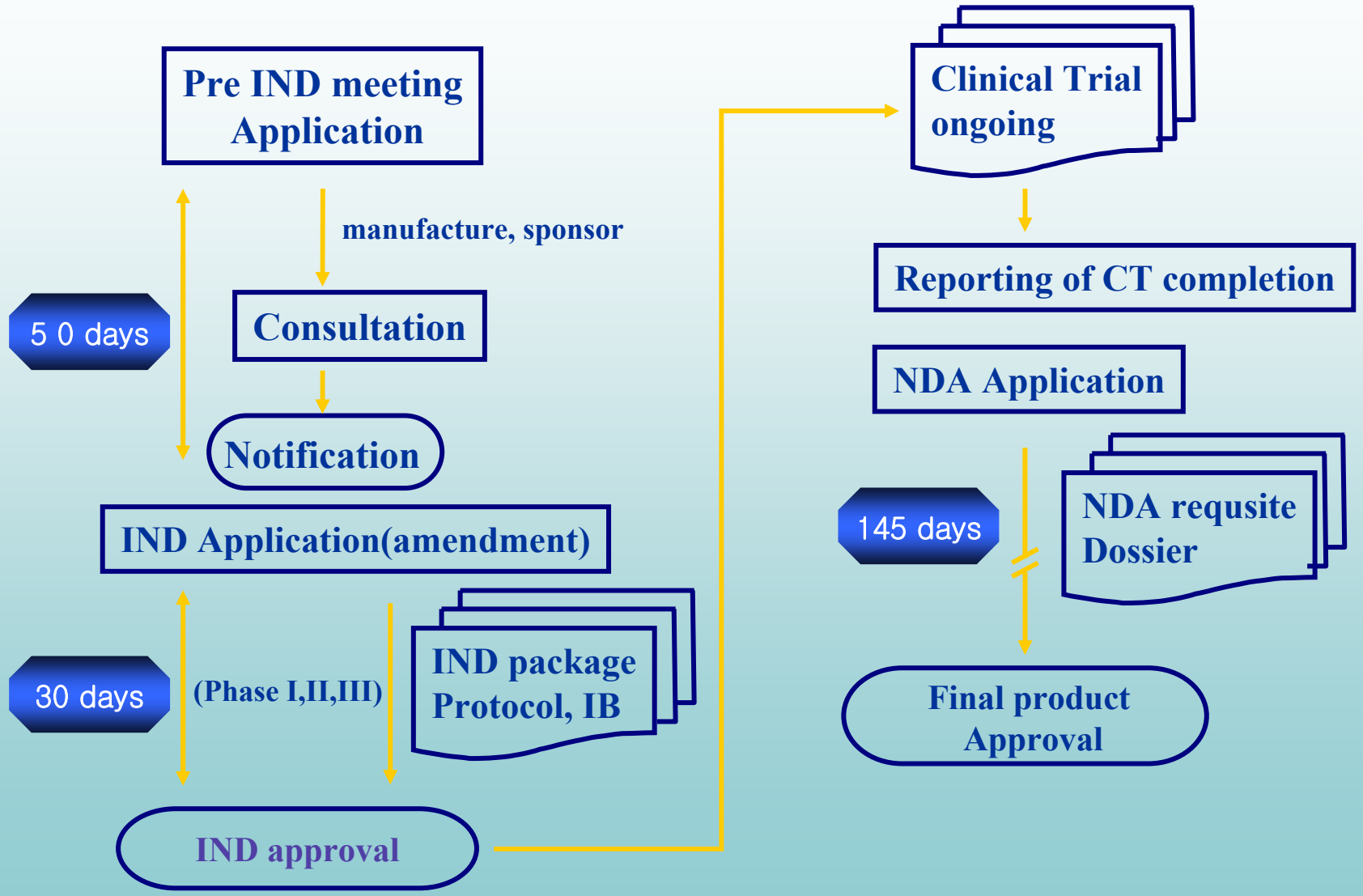
    : conducted because of an issue such as recalls, field alerts or adverse reactions
- **Regional KFDA participates the GMP inspection**

GCP 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



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'

Reporting System for AEFI

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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

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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

Timeline :30days

IRB Process

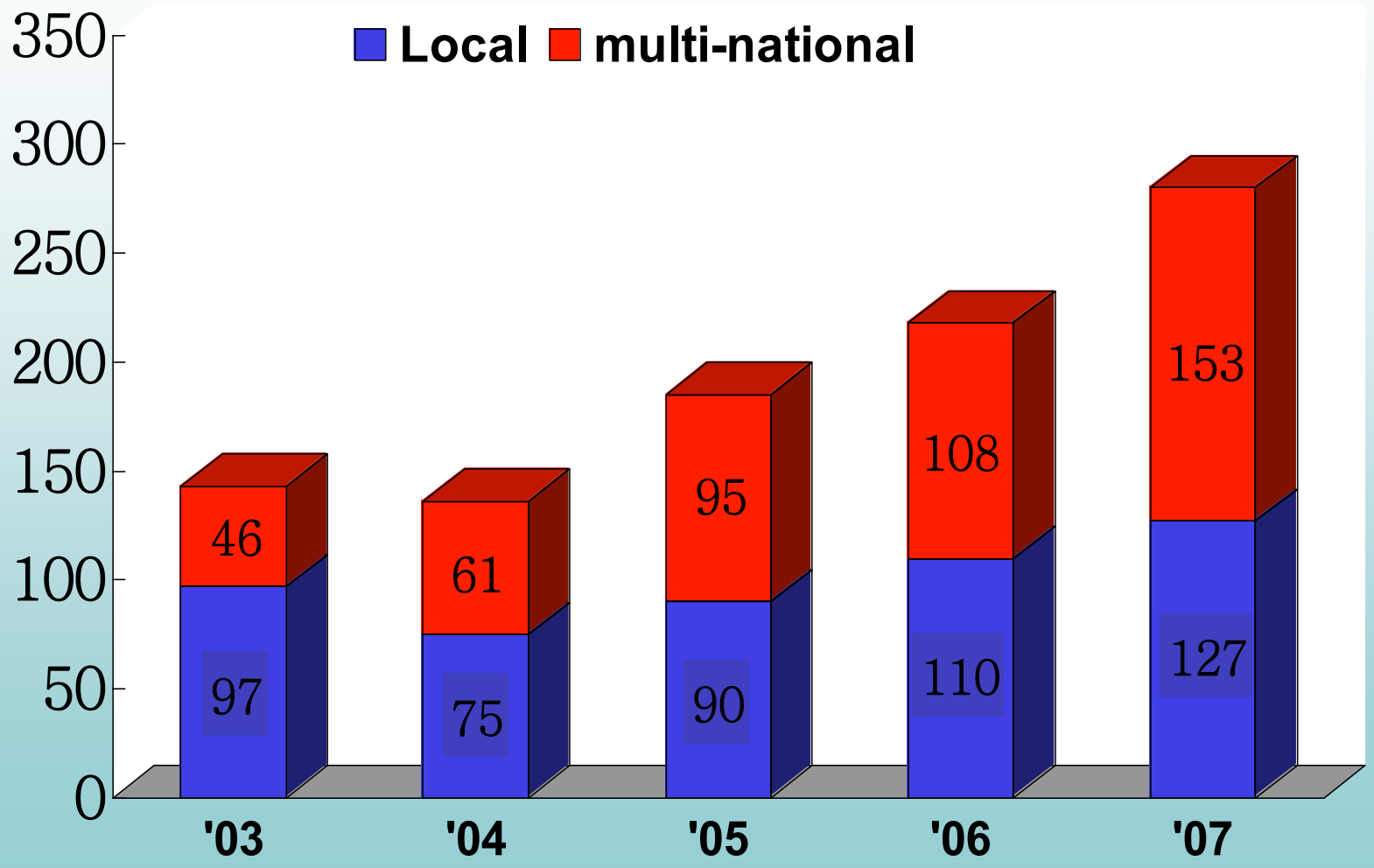
Parallel review with KFDA process

Submission → Review → Approval

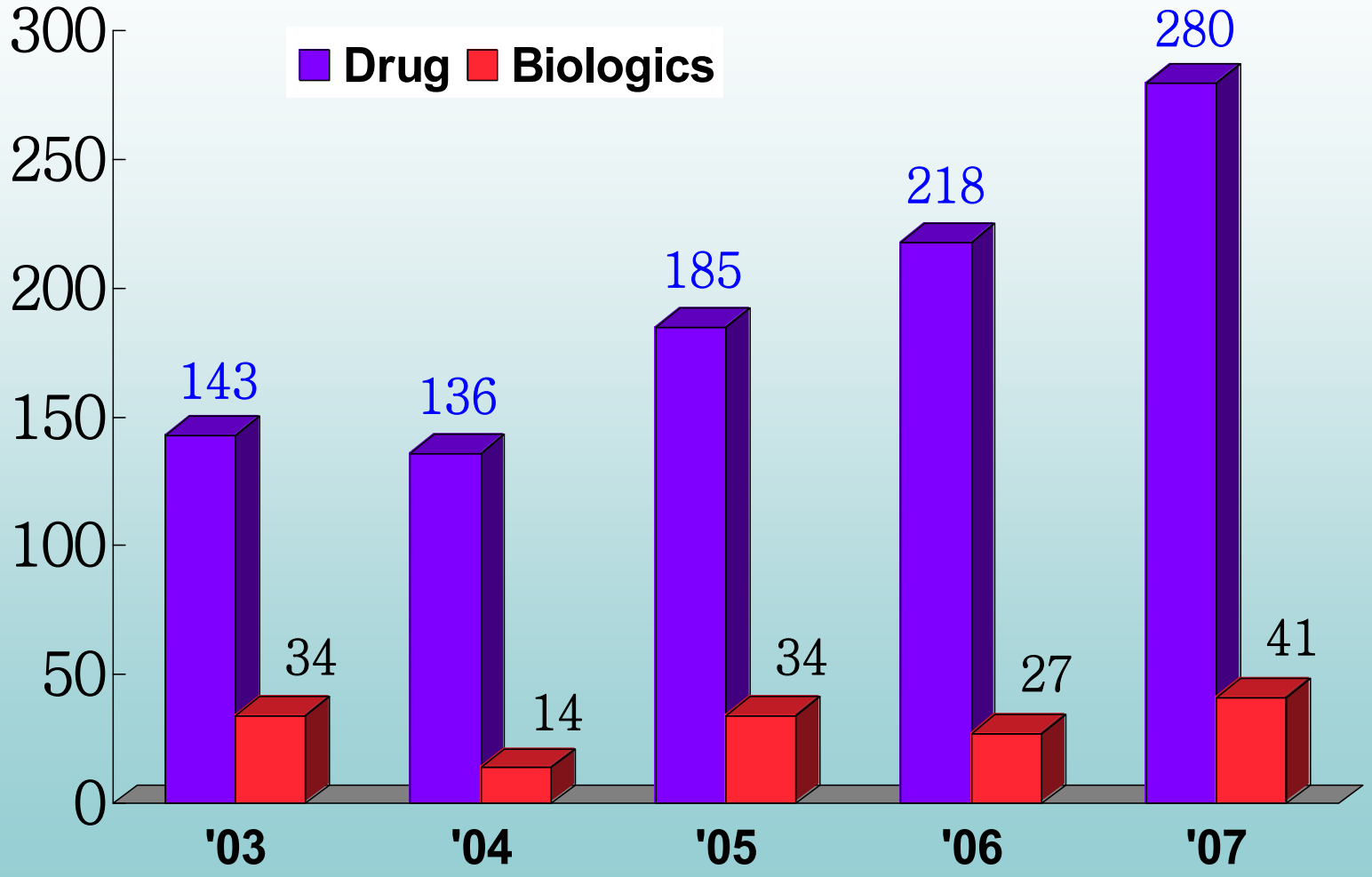
- CV
- Protocol
- IB
- CRF

Contract with Hospital

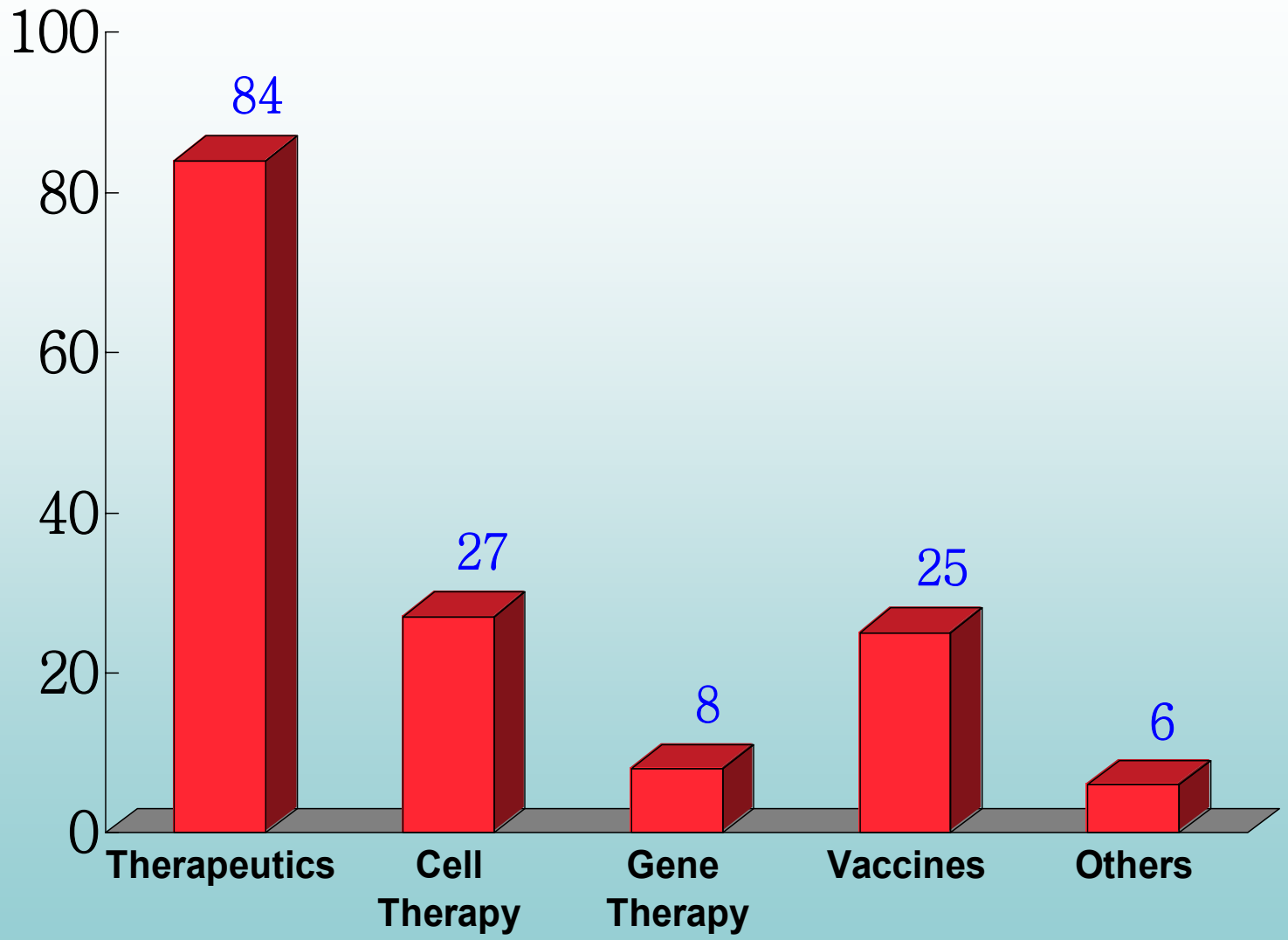
Clinical Trials Approved in KFDA



Clinical Trials Approved in KFDA



Clinical Trials Approved of Biologics ('03-'07)



Clinical Trials in Korea

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http://ezdrug.kfda.go.kr

	A	B	C	D	E	F	G
1	신청자	제품명	성분명	승인일	기관명	시험제목	단계
2	에스케이케미칼	염산날푸라핀	염산날푸라핀	2008-01-02	서울대학교병원	혈액투석환자 중 기존소양증 치료에 저항성을 나타내는 환자에서 TRK-820의 유효성 및 안전성을 평가하기 위한 이중눈가림, 무작위배정, 위약대조, 병행, 다기관 제3상 임상시험	3상
3	한국화이자제약	인스프라	에플러레논	2008-01-02	삼성서울병원 연세대세브란스병원 아주대학교병원	NYHA CLASS II의 만성 수축기 심부전 피험자에서 심혈관 사망 및 심부전 입원에 대한 EPLERENONE 대 위약의 효과	3상
4	동아제약	DA-8159	DA-8159	2008-01-02	서울대학교병원	간장애 환자와 건강한 자원자에서 udenafil의 약동학적 특성을 평가하기 위한 임상시험	1상
5	한국베링거인겔하임	BIBR 1048 MS캡슐 110, 150mg	Dabigatran Exetilate	2008-01-03	미정	급성 증후성 정맥 혈전색전증에 대해 승인된 비경구적 항응고제로 초기에 5일 이상 치료한 후 6개월 동안 투여된 경구용 dabigatran etexilate (150 mg 1일 2회)의 유효성 및 안전성을 와파린(INR 2.0~3.0)과 비교하여 평가하기 위한 제 3상 무작위배정, 이중맹검, 평행군 임상시험	3상

Regulation of Cell Therapy Products

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- Cell therapies are products composed of human or animal cells or from physical parts of those cells

- Regulated as Biologics under 'Pharmaceutical Affairs Act' from 2001

- 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

Product	Cell Type	Indication	Status
Chondron	Chondrocyte (auto)	Articular cartilage defects	NDA-approved ('01)
Articel	Chondrocyte (auto)	Articular cartilage defects	NDA-approved ('02)
Holoderm	Keratinocyte (auto)	Burn wounds	NDA-approved ('02)
Kaloderm	Keratinocyte (allo)	Burn wounds	NDA-approved ('05)
Adipocel	Adipocyte (auto)	Treatment of scar	NDA-approved ('07)

Cell Therapy Products under Clinical Trial after M.A.

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Product	Cell Type	Indication	Status
Hyalograft 3D	Fibroblast (auto)	Diabetic Foot Ulcer	MA (Phase 3)
Autocel	Keratinocyte (auto)	Burn wounds	MA (Phase 3)
Inno-LAK	Activated Lymphocyte (auto)	Lung Cancer	MA (Phase 3)
Immunecell-LC	Activated Lymphocyte (auto)	Liver Cancer	MA (Phase 3)
Cravat-RCC	Dendritic cell (auto)	Kidney Cancer	MA (Phase 3)
NKM	Activated lymphocyte (auto)	Lymphoma	MA (Phase 3)

* M.A. : Marketing Approval

Cell Therapy Products under Clinical Trial

Product	Cell Type	Indication	Status
Ostem	Osteoblast (auto)	Fracture	Phase 3
DCVac-EPL	Dendritic cell (auto)	Lung Cancer	Phase 1/2
DCVac-IR	Dendritic cell (auto)	Colon Cancer	Phase 1/2a
Creavax-PC	Dendritic cell (auto)	Prostate Cancer	Phase 1/2a
MSC1	BM MSC (auto)	Acute cerebral infarction	Phase 3

Cell Therapy Products under Clinical Trial

Product	Cell Type	Indication	Status
Cartistem	Cord blood MSC (allo)	Chronic cartilage defects	Phase 1/2
DCVac-EPB	Dendritic cell (auto)	Mammary Cancer	Phase 1/2a
TK Cell	Activated Lymphocyte (auto)	Gastric Cancer Colon Cancer	Phase 2
Myocell	Myoblast (auto)	Congestive Heart Failure	Phase 2
Kaloderm	Keratinocyte (auto)	Diabetic Foot Ulcer	Phase 3

Cell Therapy Products under Clinical Trial

Product	Cell Type	Indication	Status
Inno LC-01	Activated Lymphocyte (auto)	Brain Cancer	Phase 3
Cerecellgram-spine	BM MSC (auto)	Chronic Spinal Cord Injury	Phase 2/3
MSC2	BM MSC (auto)	Myocardial infarction	Phase 2/3
Vascostem	Adipose tissue cell	Buerger's Disease	Phase 1/2

Regulation of Cell & Tissue

식의약품 종합정보서비스 KIFDA

- 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 Therapy Products

- Gene therapies introduce genetic material into the human body to replace a defective or missing gene or to treat or cure disease
- Regulated as Biologics under 'Pharmaceutical Affairs Act' from 1999
- There is no approved gene therapy product in Korea
- 8 products under clinical trial

Gene Therapy Products under Clinical Trial

Product	Indication	Status	Vector (gene)
VMDA3601	Ischemic Foot Ulceration	II	Plasmid DNA (VEGF)
GX-12	HIV Infection	I	Plasmid DNA (Ag & IL-12)
JX-594	Liver Cancer	I	Vaccinia virus (TK^- & CSF)
VM206RY	Ischemic Heart Disease	I	Plasmid DNA (HGF)
TissueGene-C	Osteoarthritis	I	Retrovirus (TGF-β)
VM106	Chronic Granulomatus Disesase	I/IIa	Retrovirus (gp91)
Theragene	Prostate Cancer	II	Adenovirus (TK & CD)
HB-110	Chronic Hepatitis B	I	Plasmid DNA (Ag & IL-12)

Biochips Approved in Korea

Product	Indication	Manufacturer	Approved
HPV DNA chip	Diagnosis for HPV	Biomedlab	**'04**
MyHPV	Diagnosis for HPV	Mygene	**'04**
Macrogen BAC Chip H 1440	Genetic diagnosis	Macrogen	**'06**
Goodgene HPV DNA Genotyping Chip	Diagnosis for HPV	Goodgene	**'07**
HPV Genotyping chip	Diagnosis for HPV	Biocore	**'07**

Future Challenges

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- **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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