East Asian Pharmaceutical Regulatory Symposium 2008

EAPRS 2008

KFDA

Latest Trend of Drug Quality in Korea

2008. 4.14

In-Kyu Kim, Ph.D.
Division Director
Drug Evaluation Department

Contents

- Status of KFDA
- CMC, GRP and CTD
- DMF
- GMP
- Quality Control on the market
- International Harmonization

History of KFDA

1945 National Chemistry Laboratory (NCL)

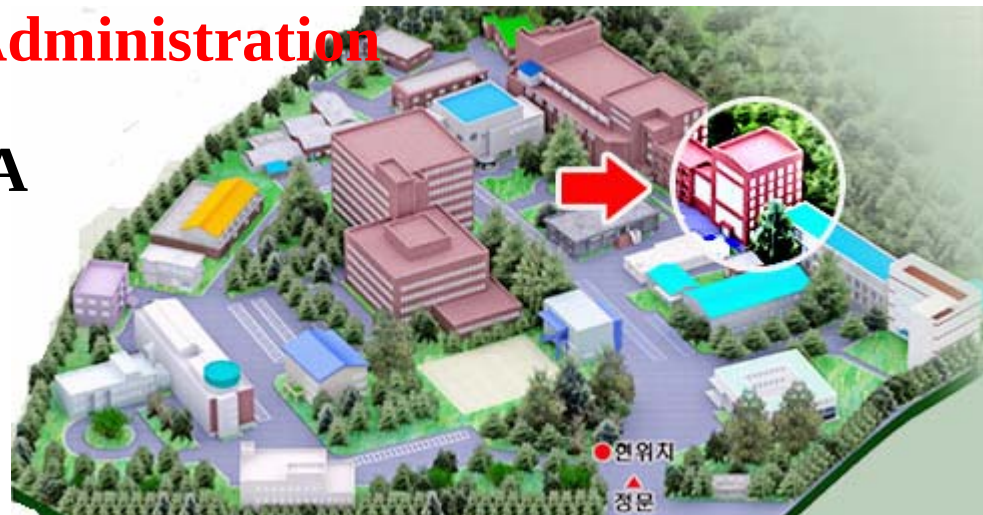
1959 National Institute of Health (NIH)

1987 The National Institute of Safety Research (NISR)

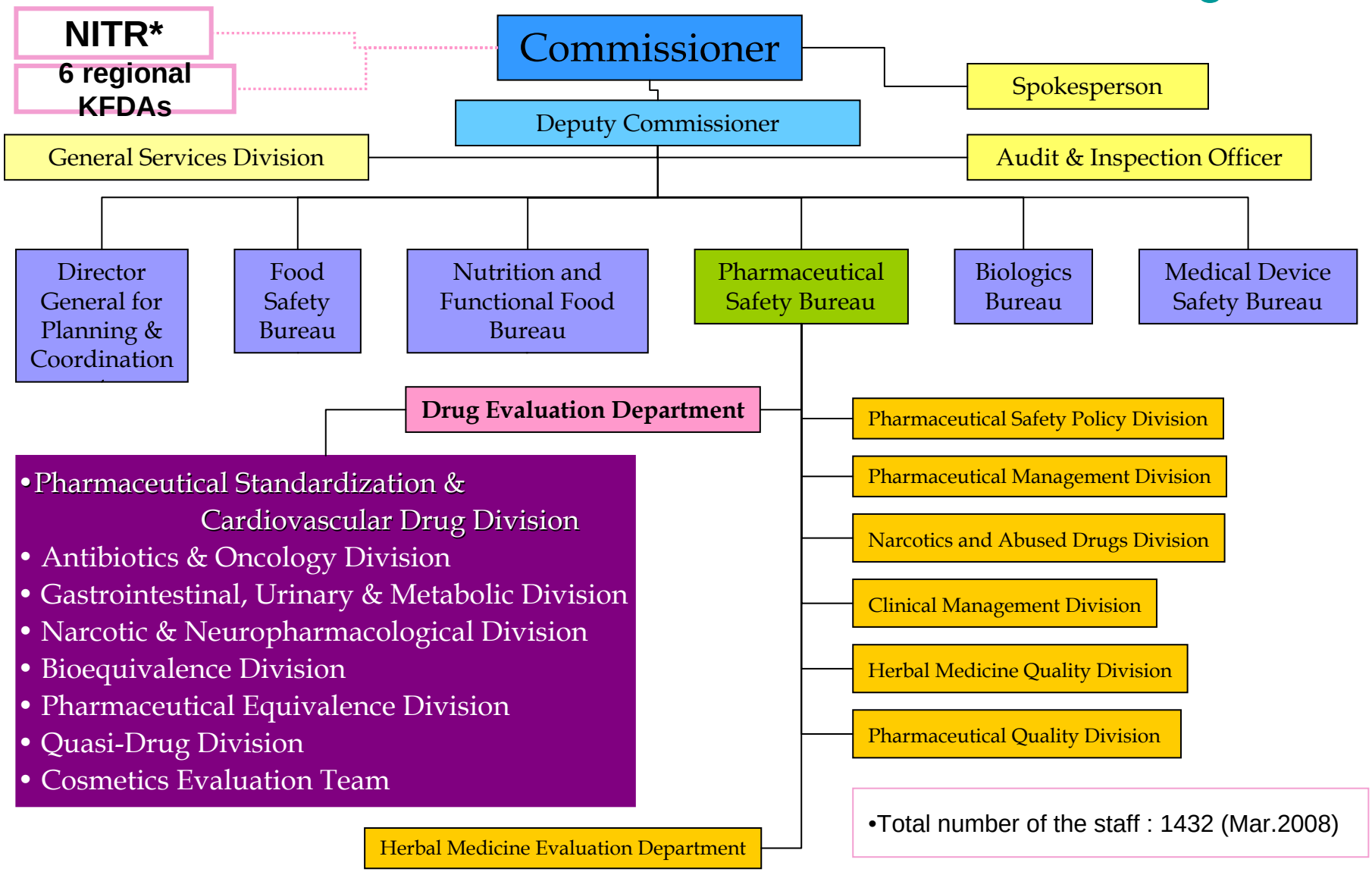
1996 Korea Food and Drug Safety Headquarter

1998 Korea Food and Drug Administration

2004 Reorganization of KFDA



Organization Chart of KFDA



Human Resources of KFDA

○Total : 1432 (Mar. 2008)

- Main Campus : 665, NITR : 137 Regional : 630

○ Pharmaceutical Safety Bureau 175

- 6 Divisions

- Drug Evaluation Department (8 Divisions)79

- Herbal Medicine Department (3 Divisions) 29

○ Biological Safety Bureau 84

○ Medical Devices Safety Bureau : 75

Life Science Complex at Osong

Equal Development of the Country

Localization of government agencies

Moving in 2010

Bird's eye-view of New Complex

Korea Food and Drug Administration (KFDA)

National Institute of Toxicological Research (NITR)

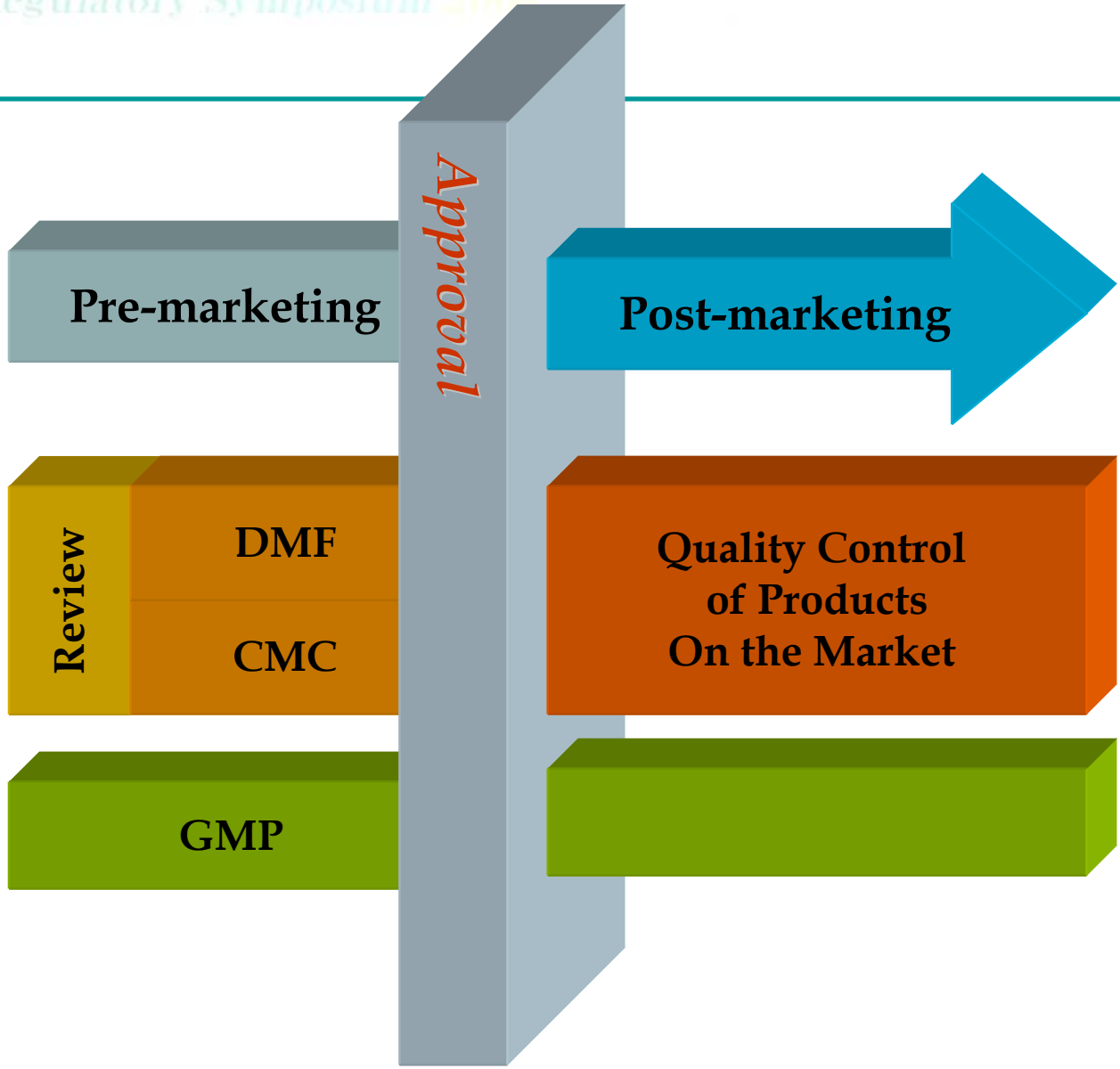
Center for Disease Control (CDC), National Institute of Health (NIH)

The Korea Health Industry Development Institute (KHIDI)

Korea Human Resources Development Institute for Health and Welfare (KHRDI)

History of Pharmaceutical Environment

1950-1970	1980s	1990s	2000s
		GMP(1994) GCP(1995) GLP(1997)	cGMP(2008) GSP DMF(2002) IND (2002) GRP(2004) CTD(2009)
Early Step of Pharmaceutical Industry	Concern of NME Development	Start of NME Development	NME Development

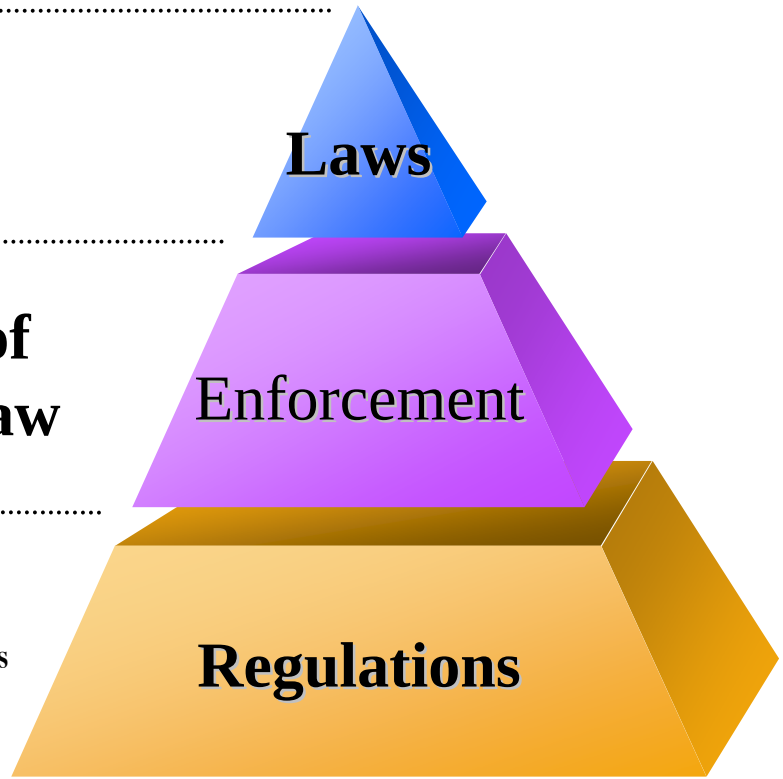

Approval
Pre-marketing
Post-marketing
Review
DMF
CMC
Quality Control of Products On the Market
GMP

Regulatory Hierarchy

Pharmaceutical Affairs Law

The Enforcement Regulation of the Pharmaceutical Affairs Law

1. The Regulation for Approval of Manufacturer and Manufacture (Import) of Drugs
2. The Regulation for Evaluation on the Safety and Efficacy of Drugs
3. The Regulation for Specifications and Test Procedures of Drugs
4. The Regulation of Clinical study protocol approval process



Pharmaceutical Law and Regulations

- **The Pharmaceutical Affairs Law**
- **The Enforcement Regulation of the Pharmaceutical Affairs Law**

- **The Regulation for Approval of Manufacturer and Manufacture (Import) of Drugs**
- **The Regulation for Evaluation on the Safety and Efficacy of Drugs**
- **The Regulation for Specifications and Test Procedures of Drugs**
- **The Regulation of Clinical study protocol approval process**

Pharmaceutical Guidelines

- **Guideline for nomenclature of drugs**
- **Guideline for test method validations**
- **Guideline for residual solvents**
- **Guideline for dissolution testing of solid oral dosage forms**
- **Guideline for preparation of specification and test method documents of narcotics diagnosis kit**

Review of Chemistry, Manufacturing & Control (CMC)

Pharmaceutical Standards

- **Korea Pharmacopoeia 9th Ed.(in Korean) 2007.12**
- **Korea Pharmacopoeia 9th Ed.(in English) 2008.12**

- **Korean Pharmaceutical Codex 3rd Ed. (2007)**

- **Antibiotics Standards (2007)**

Data Requirements for Quality Evaluation of NDA, ANDA

- Origin or discovery & pharmaceutical development
- Data on use in local or foreign countries
- Data on drug substances
  - Structural characterization
  - Physical and chemical characterization
  - Manufacturing process
  - Justification of specification & analytical procedures
  - Batch analysis
  - Reference standards and reagents
- Data on drug products
  - Components of drug product (including control of excipients)
  - Manufacturing process
  - Justification of specification & analytical procedures
  - Batch analysis
  - Reference standards and reagents

KFDA's Good Review Practices

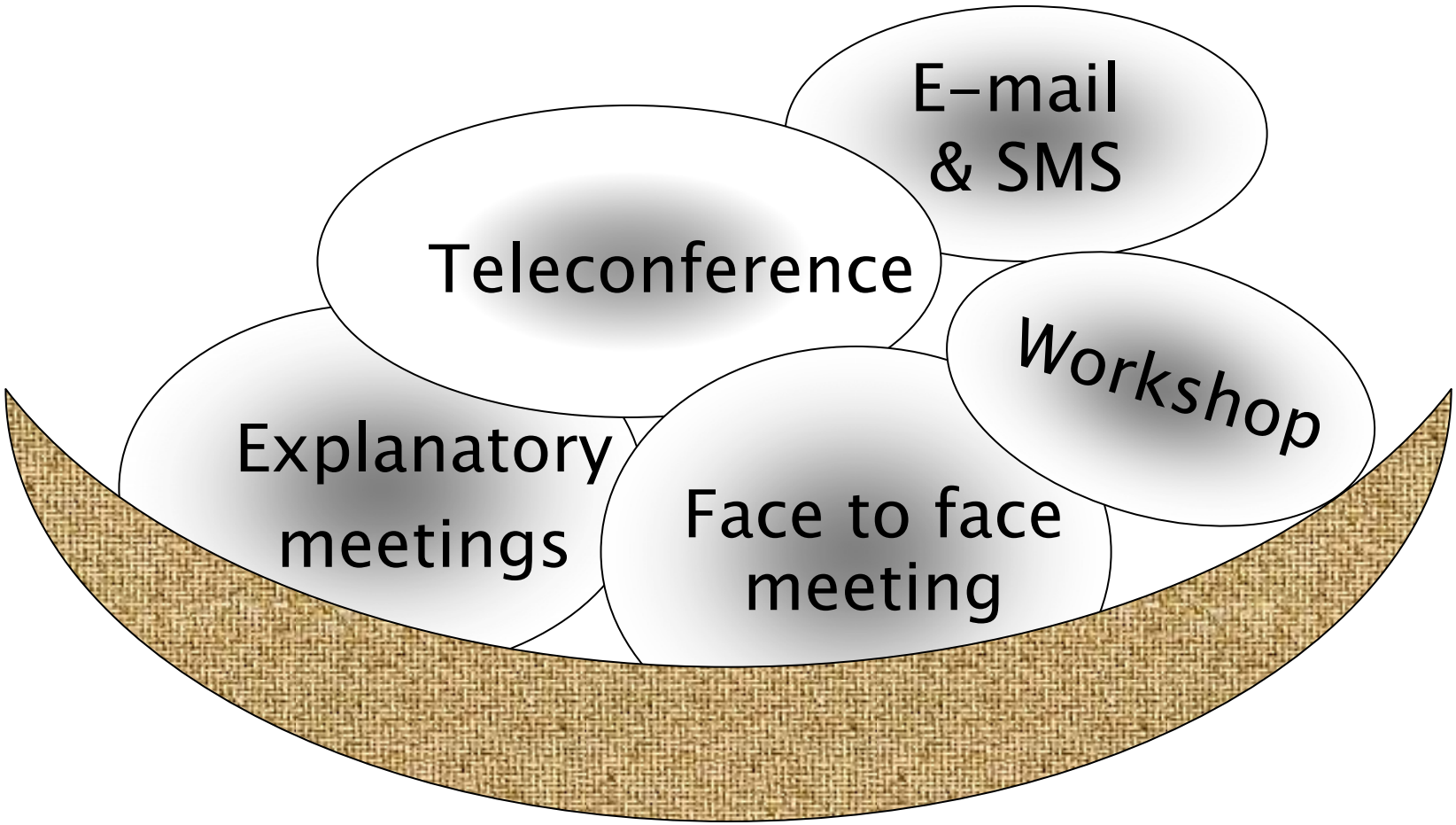
- After 2004.2.4., KFDA has engaged in the Good Review Practices
- Objective
  - Recognize that format influences content by imposing a logic to the review
  - Builds in quality by shaping both the conduct of the review and the presentation of the review results
  - Guarantee of quality, efficiency, clarity, transparency, consistency of the review results

KFDA's Good Review Practices

- Review template for CMC, DMF, Pharm/Tox and clinical data review
- Training programs for reviewer
  - Clinical Trial Course
  - Seminar
  - Workshop
  - Symposium
- Disclosure of Review Results

- Dialogues between customers and the KFDA
  - Internal experts meeting
  - External advisory committee

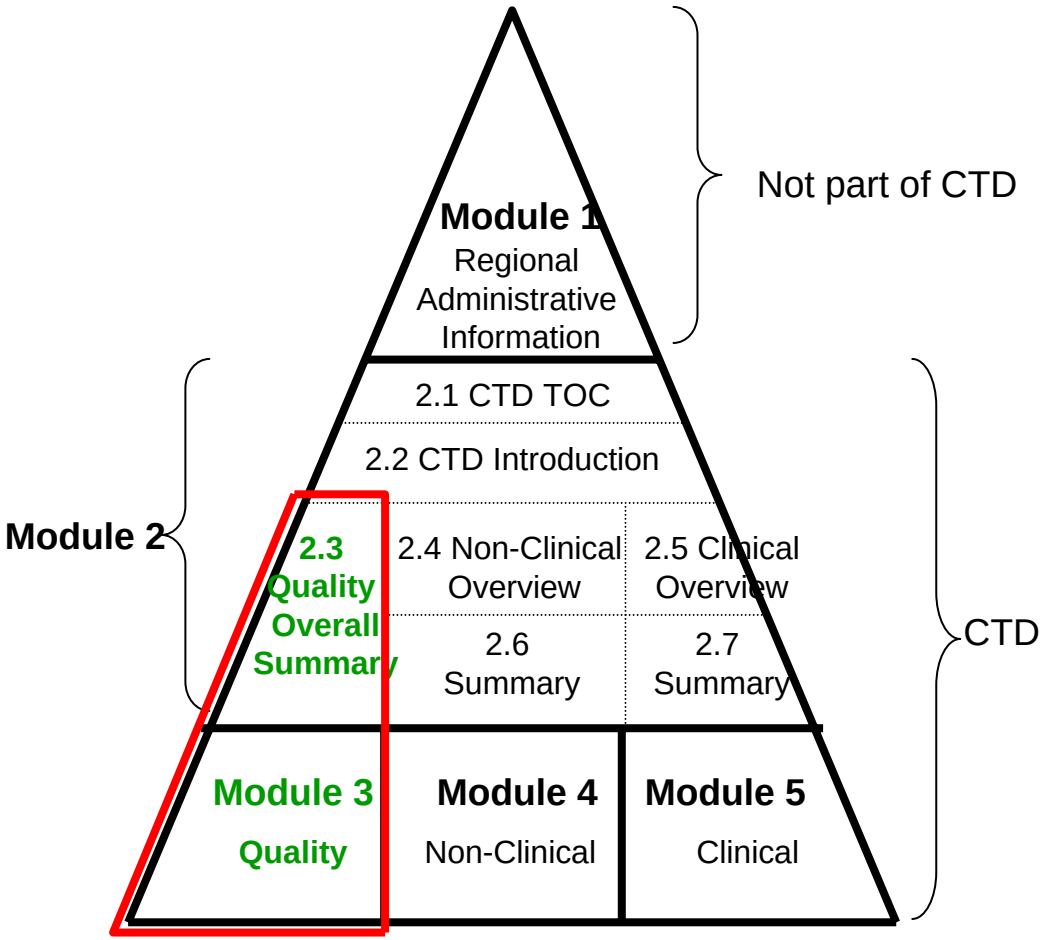
Dialogues between customers and the KFDA



Introduction of CTD

- CTD
  - March 2009 : New chemical entities
  - March 2010 : A drug product that is not new but subject to review of safety and efficacy
    - New formulation, new combination of 2 or more active ingredient, increase or decrease in strength, new salts or isomers, new indication

CTD Organization: Diagrammatic Representation



5 Modules

Module 1 Regional Requirements (EU/FDA/MHLW)
Module 2 Summary
Module 3 Quality
Module 4 Non-Clinical
Module 5 Clinical

Note: Additional regional requirements are also specified in each Module 2-5.

CTD related to Quality

3.1 Table of Contents

3.2 Body of Data

- 3.2.S Drug Substance
  - 3.2.S.1 General Information
  - 3.2.S.2 Manufacture
  - 3.2.S.3 Characterization
  - 3.2.S.4 Control of Drug Substance
  - 3.2.S.5 Reference Standard
  - 3.2.S.6 Container Closure System
  - 3.2.S.7 Stability

CTD related to Quality

- **3.2.P DRUG PRODUCT**
  - **3.2.P.1 Description & Composition**
  - **3.2.P.2 Pharmaceutical Development**
  - **3.2.P.3 Manufacture**
  - **3.2.P.4 Control of Excipients**
  - **3.2.P.5 Control of Drug Product**
  - **3.2.P.6 Reference Standard**
  - **3.2.P.7 Container Closure System**
  - **3.2.P.8 Stability**
- **3.2.A Appendices**
  - **3.2.A.1 Facilities and Equipment**
  - **3.2.A.2 Adventitious Agents**
  - **3.2.A.3 Novel Excipients**
- **3.2.R Regional Information**
- **3.3 Literature References**

Drug Master File (DMF)

KDMF Introduction

KDMF : API registration system
(effective as of July 1st, 2002)

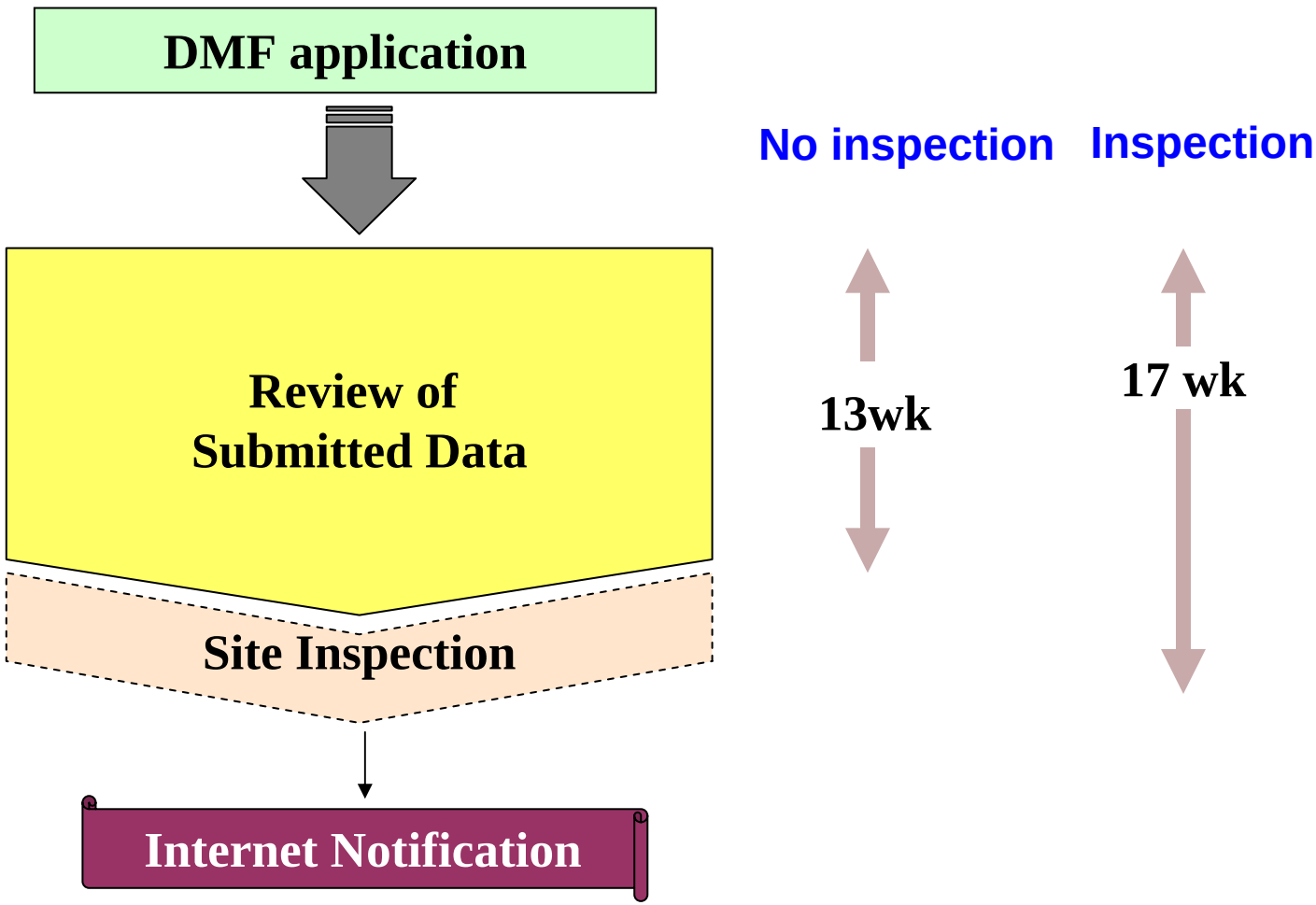
- **Background**
  - Concerns about using low quality of drug substances
  - Quality control of drug substances
- **Scope**
  - New chemical entities used as APIS
  - Phase-in of other APIs registration

 # Only drug substances registered can be used.

Chronology

- 2002 : API for new chemical entities
- 2005 : added 77 APIs : gliclazide etc
- 2006 : added human placenta
- 2007 : added 22 APIs : domferidone etc
- 2008 : added 14 APIs : norfloxacin etc

Standard Review Procedure



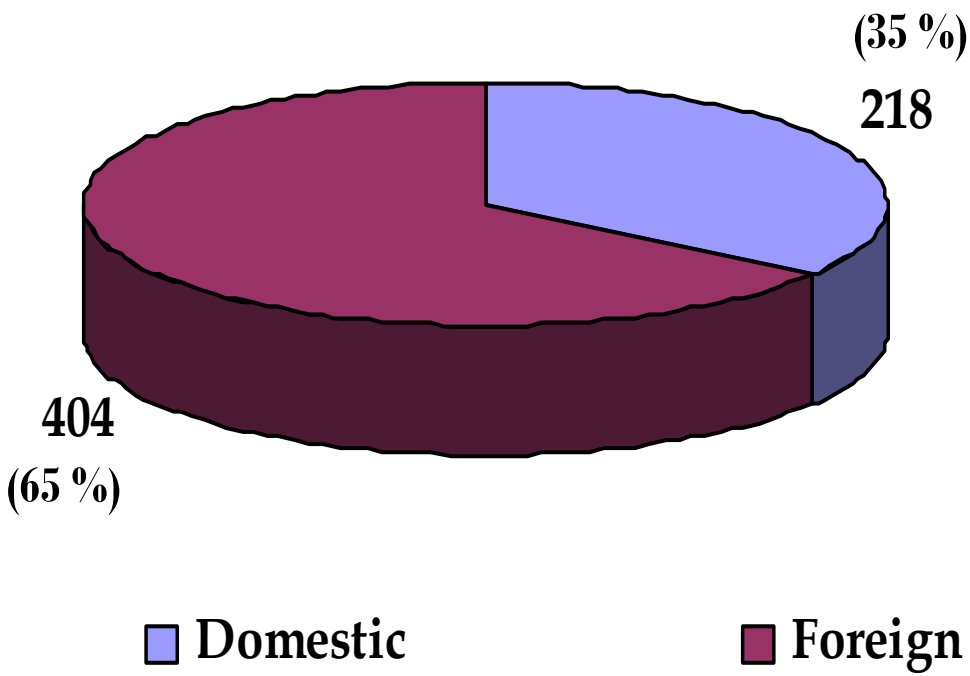
Data Requirements for DMF Review

1. Data on facilities of manufacturing site
2. Data on physico-chemical properties and stability
3. Manufacturing process, packaging, containers and cautions, etc.
4. GMP certificate or documents required for GMP application
5. Data on batch analysis, analytical methods, and used solvents
6. Samples

For the detail requirements, please see here →

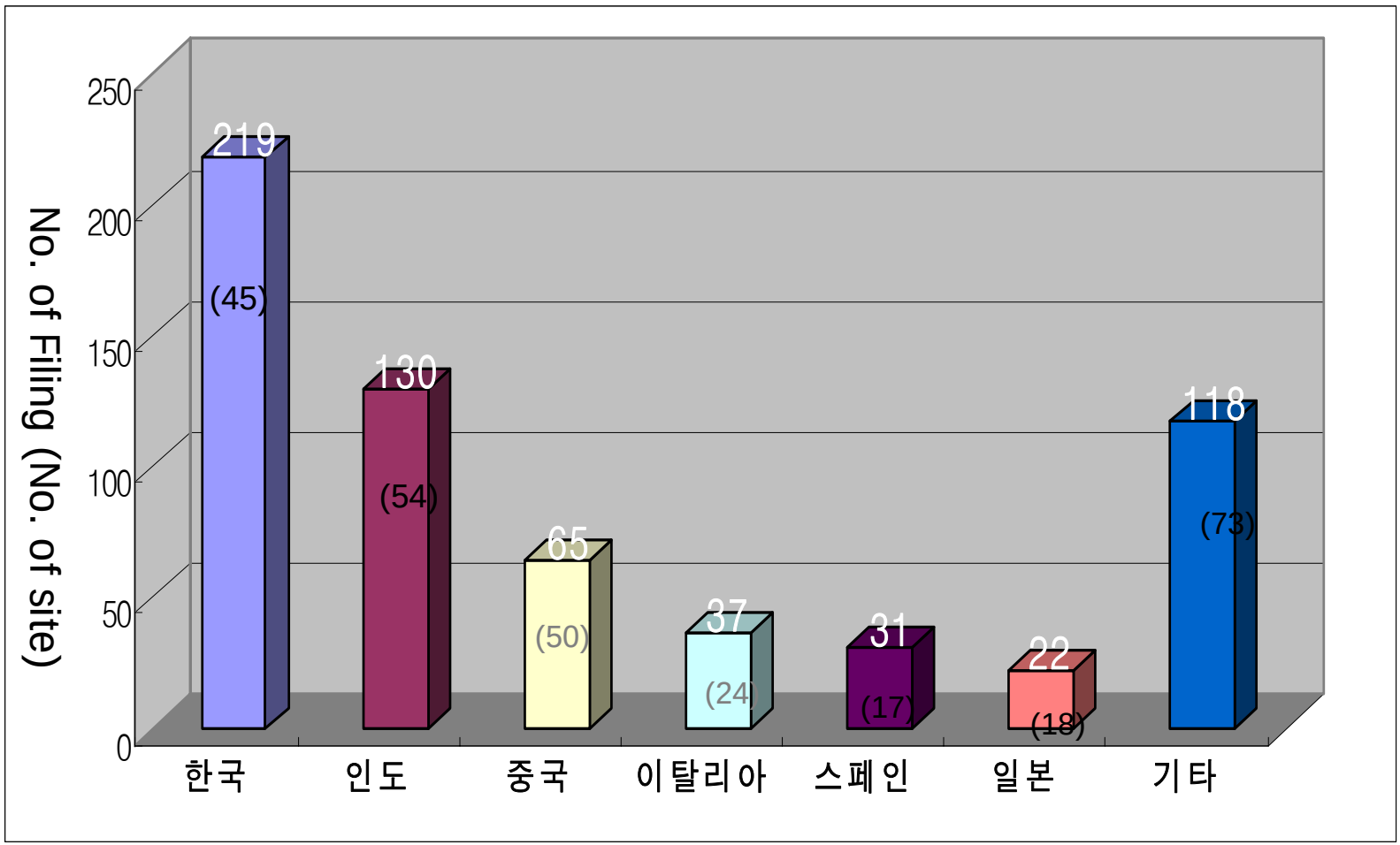
Microsoft Word Document

Ratio of APIs (Domestic vs Foreign)



77 APIs (Total 622 items)

77 APIs filed



Unit : APIs (Manufacturers)

Manufacturing Plant Inspection

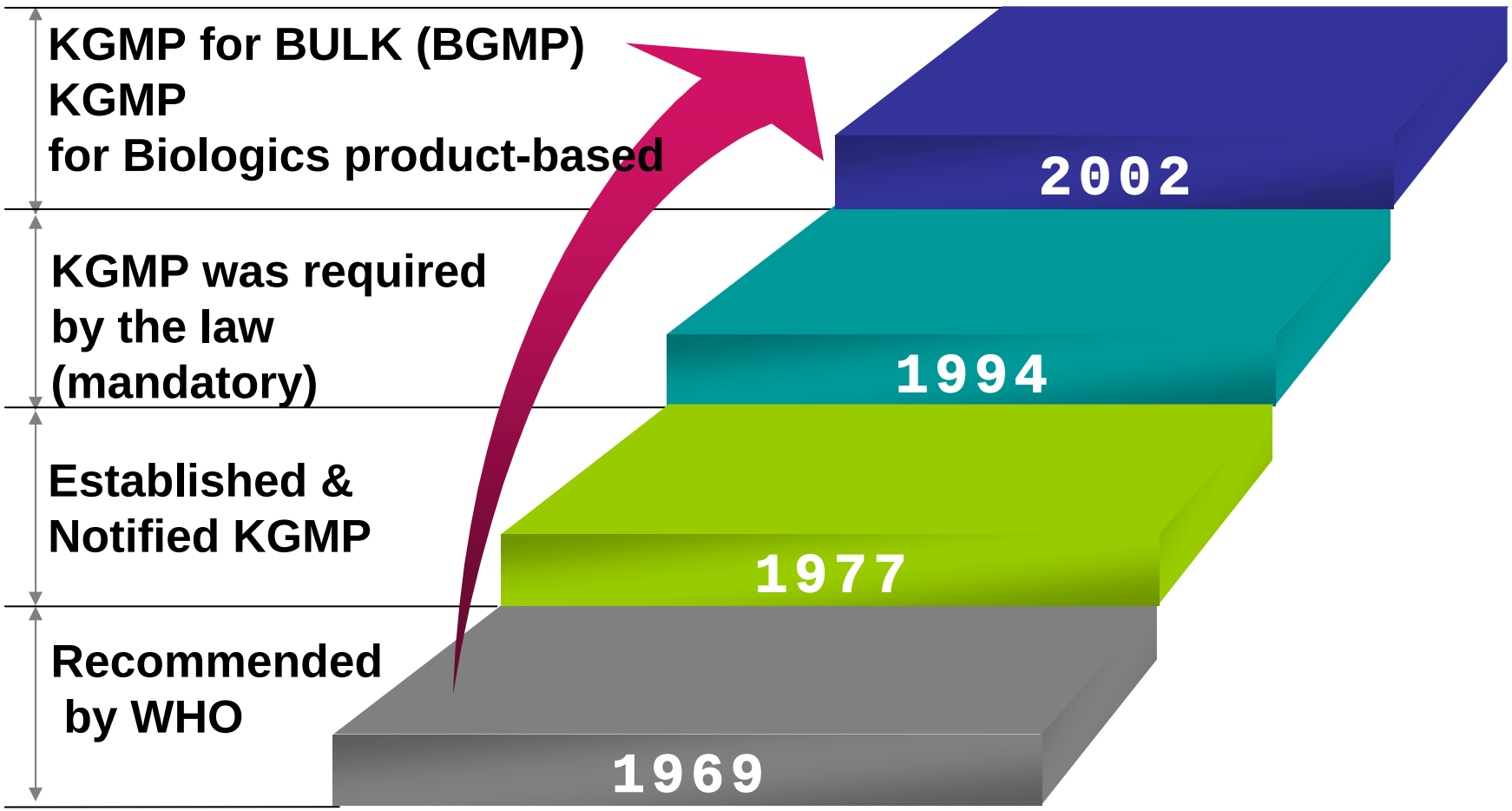
- **Before a drug substance is registered, KFDA officers conduct inspections of domestic and foreign plants**

- **Inspection waiver before a drug registration**
  - **Manufacturing plant previously accepted by KFDA DMF inspection**
  - **Submitting GMP certification (or US FDA EIR, etc) including the drug name of ICH countries**
  - **Submitting GMP certification of international authorization Organization (ex: EDQM, WHO, EMEA)**
    - **Inspection report including the drug name**

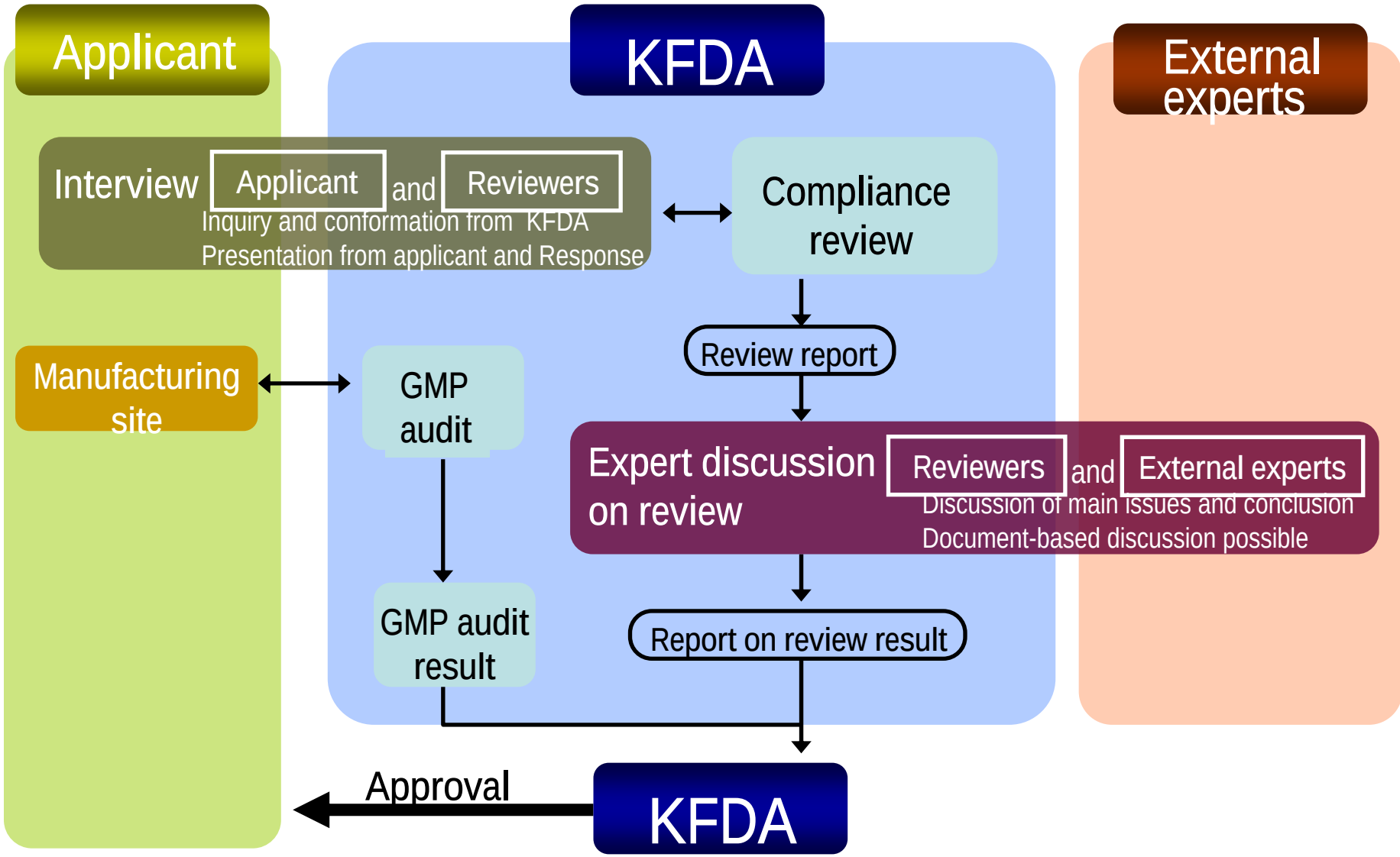
**** Exception a sterile drug, a drug manufactured by fermentation process and etc.***

Good Manufacturing Practice (GMP)

Milestone of GMP in Korea



Flow Chart of GMP Approval in Korea



Current status

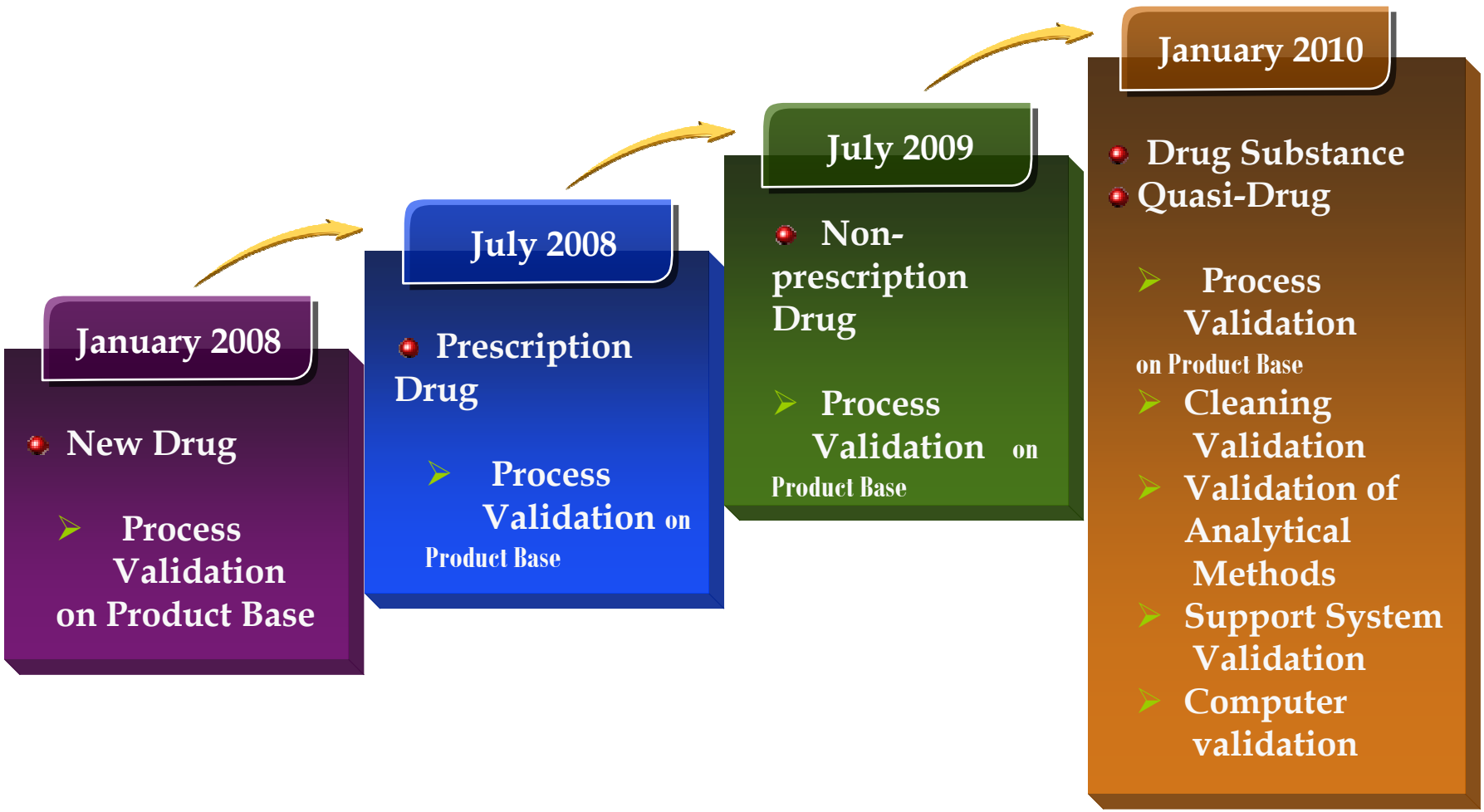
- 120 days for review and inspection
- GMP management by formulation (Not by product)
- Optional GMP education for manufacturer (Not mandatory)
- Authorization of GMP facility & operation system by document review & inspection
- Lack of GMP rules for herbal medicine
- Lack of GMP rules for clinical trial medicine
- Validation (Recommendation)

Revision of KGMP Regulation

- Background
  - To improve the current KGMP to the international level
  - Korean pharmaceutical companies could be internationally competitive
  - International collaboration on GMP like PIC/S

- Major Changes
  - Pre-approval KGMP (Product-based)
  - Process Validation

Road Map for GMP Upgrade



Process Validation

- Prospective Validation for critical processes of each product that could impact on the product quality
- Concurrent or Retrospective validation could be considered in limited cases.
- Categories
  - Prospective Validation
    - Consecutive 3 lots manufactured in a full scale
    - Conducted before marketing
  - Concurrent Validation
    - Consecutive 3 lots manufactured in a full scale
    - Conducted while marketing is continued – in limited cases
  - Retrospective Validation
    - Consecutive 10-30 lots manufactured in a full scale, including deviated lots
    - Review of batch records and stability data, etc.
    - No change of composition, manufacturing process & equipment
  - Re-validation
    - Conducted periodically or for major changes in drug substance, process, equipment, etc.

IND – GMP Guideline

General-KGMP		IND-KGMP
Pharmacist	**Authorized manufacturer**	Pharmacist or Non-pharmacist
Limited to Contract Unit	**Range of quality unit**	Not Limited
Mandatory	**Validation**	Optional
Mandatory	**Qualification**	Optional
3 Lot	**Quantity**	Not available

Quality Control of Products on the Market

Annual Plan

- Monitoring the quality of pharmaceutical products on the market
  - 2007 : 2,000 products
  - 2008 : 2,400 products
    - Pharmaceutical Bureau : 300 products
    - 6 Regional KFDAs : 2,100 products

International Harmonization

- Japan-China-Korea Director-General Level Meeting 2008.4.14 Japan, Tokyo
- 2008 East Asian Pharmaceutical Regulatory Symposium 2008.4.14-15 Tokyo, Japan
- 13th ICDRA meeting in Switzerland, Bern 2008.9.16-21
- 44th DIA Meeting in USA, Boston 2008.6.21-28
- US FDA's CDER Forum for International Drug Regulatory Authorities
- APEC Meeting
- ICH Meeting in USA, Oregon

Internationally Harmonized Quality System

Internationally Harmonized Quality System

Improvement of Pharmaceutical Quality System

Facilitation Science-based Quality Assessment

Comprehensive Understanding of Manufacturing Process and Products

ありがとうございます

谢谢

감사합니다.

Thank you

Inkyu Kim, Ph.D.

Drug Evaluation Department, KFDA

Phone : 82-2-380-1716

Email : inkyukim123@yahoo.com, ikkim@kfda.go.kr