



*East Asian Pharmaceutical
Regulatory Symposium 2008*



Latest Trend of Drug Quality in Korea

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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)

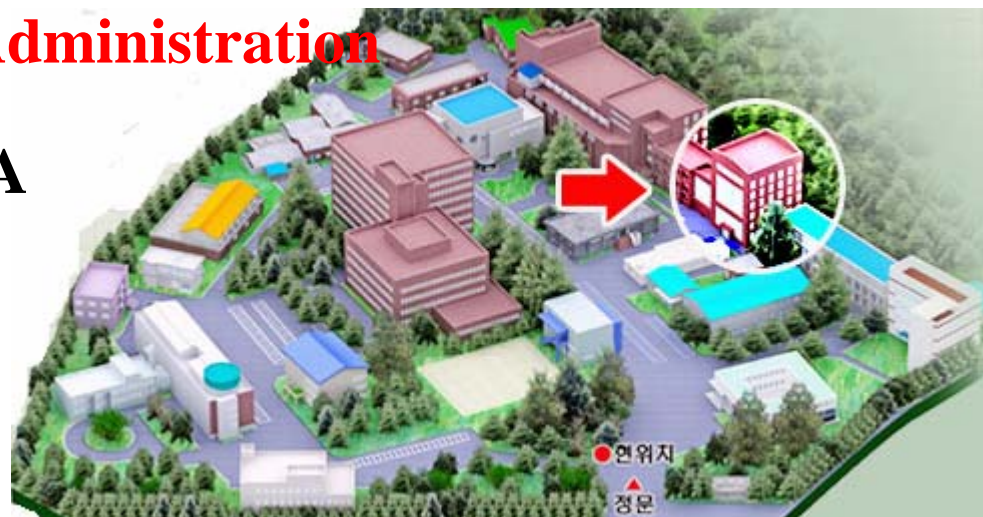
1959 National Institute of Health (NIH)

1987 The National Institute of Safety Research (NISR)

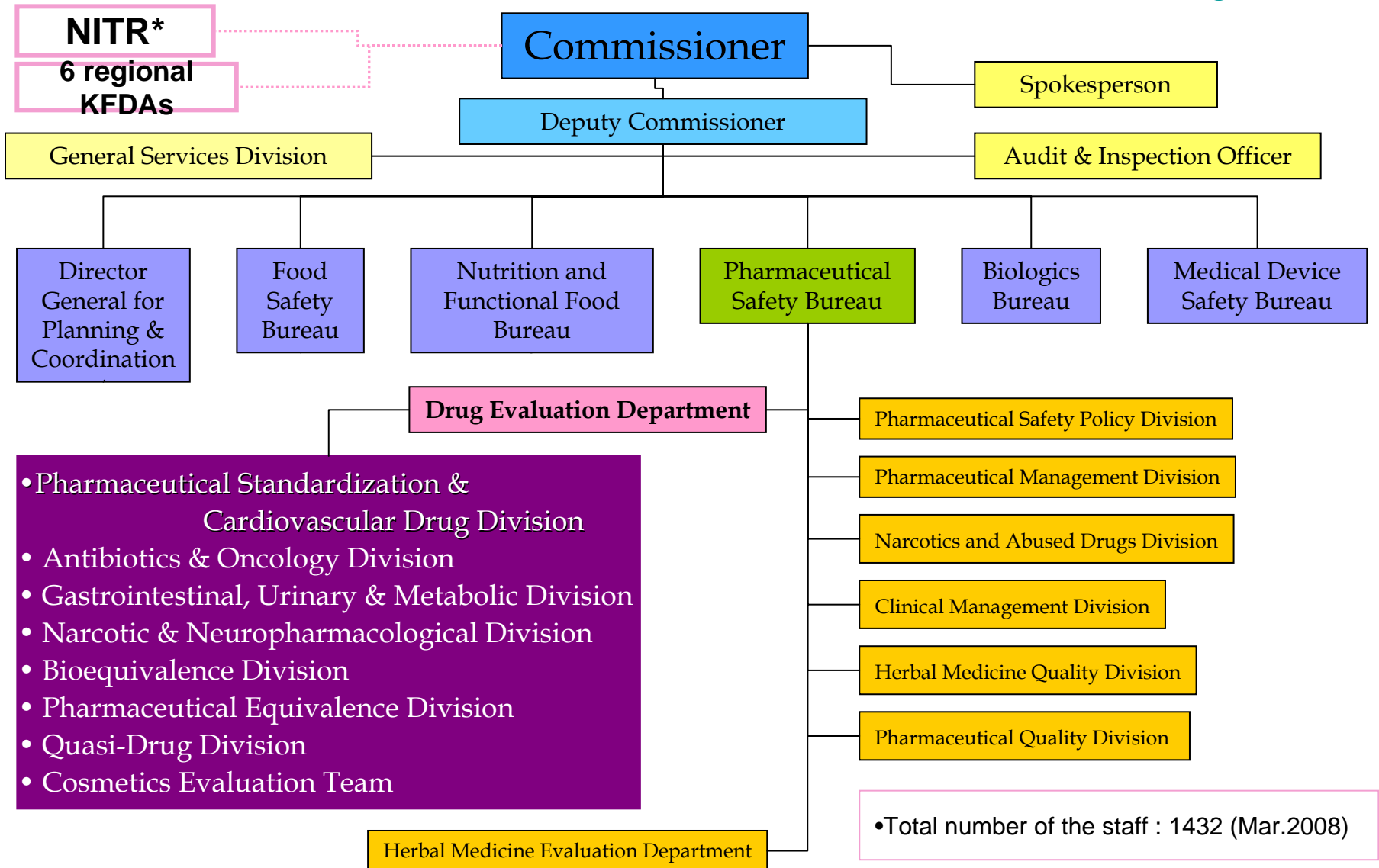
1996 Korea Food and Drug Safety Headquarter

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)

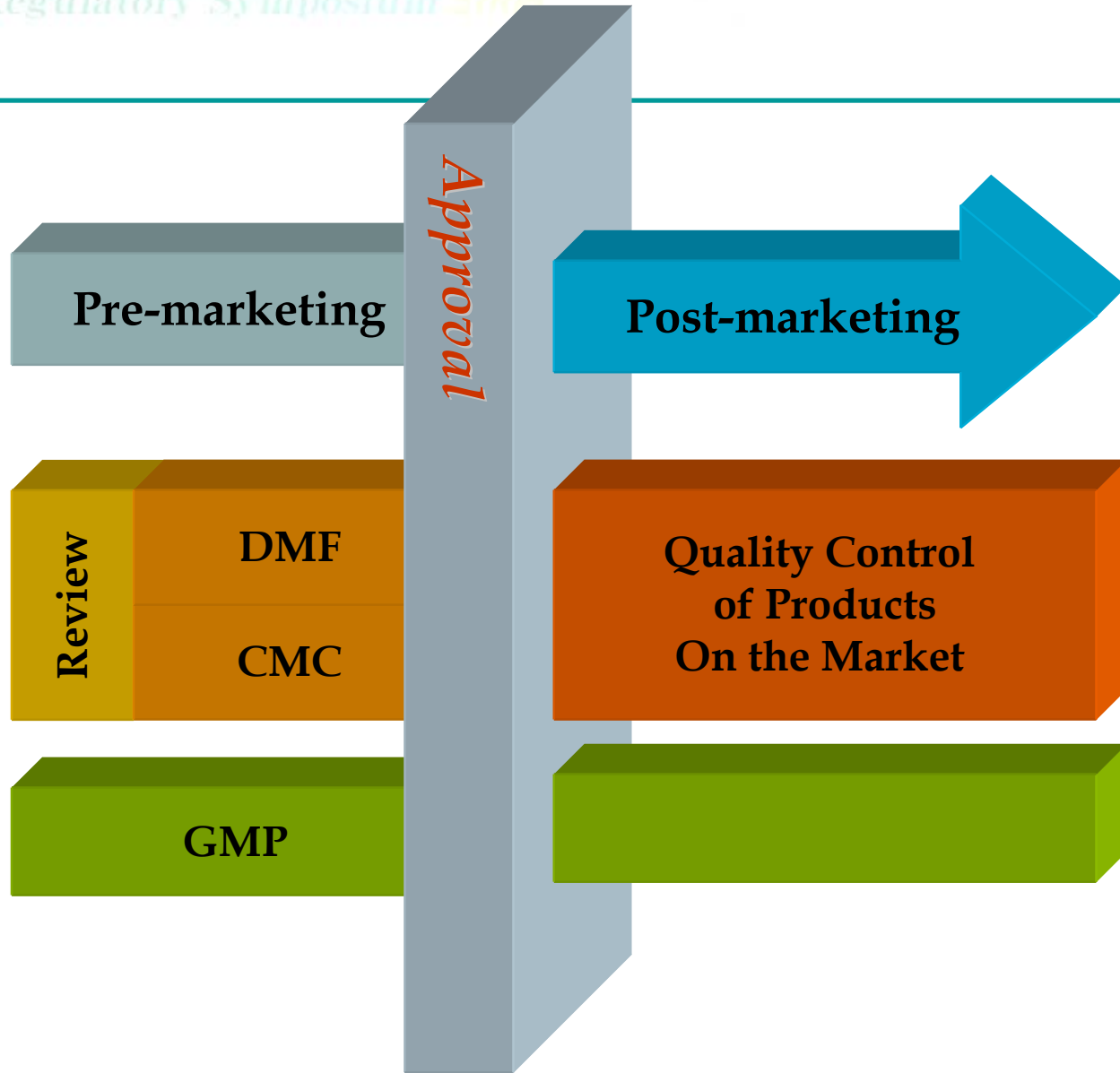
Center for Disease Control (CDC), National Institute of Health (NIH)

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 Pharmaceu tical Industry	Concern of NME Development	Start of NME Development	NME Development

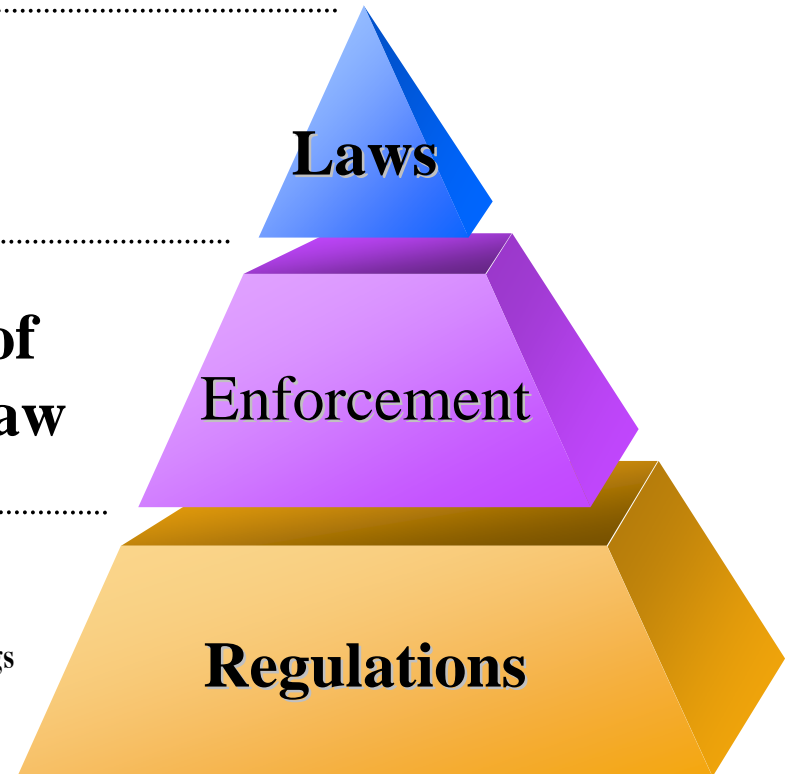


Regulatory Hierarchy

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**



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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

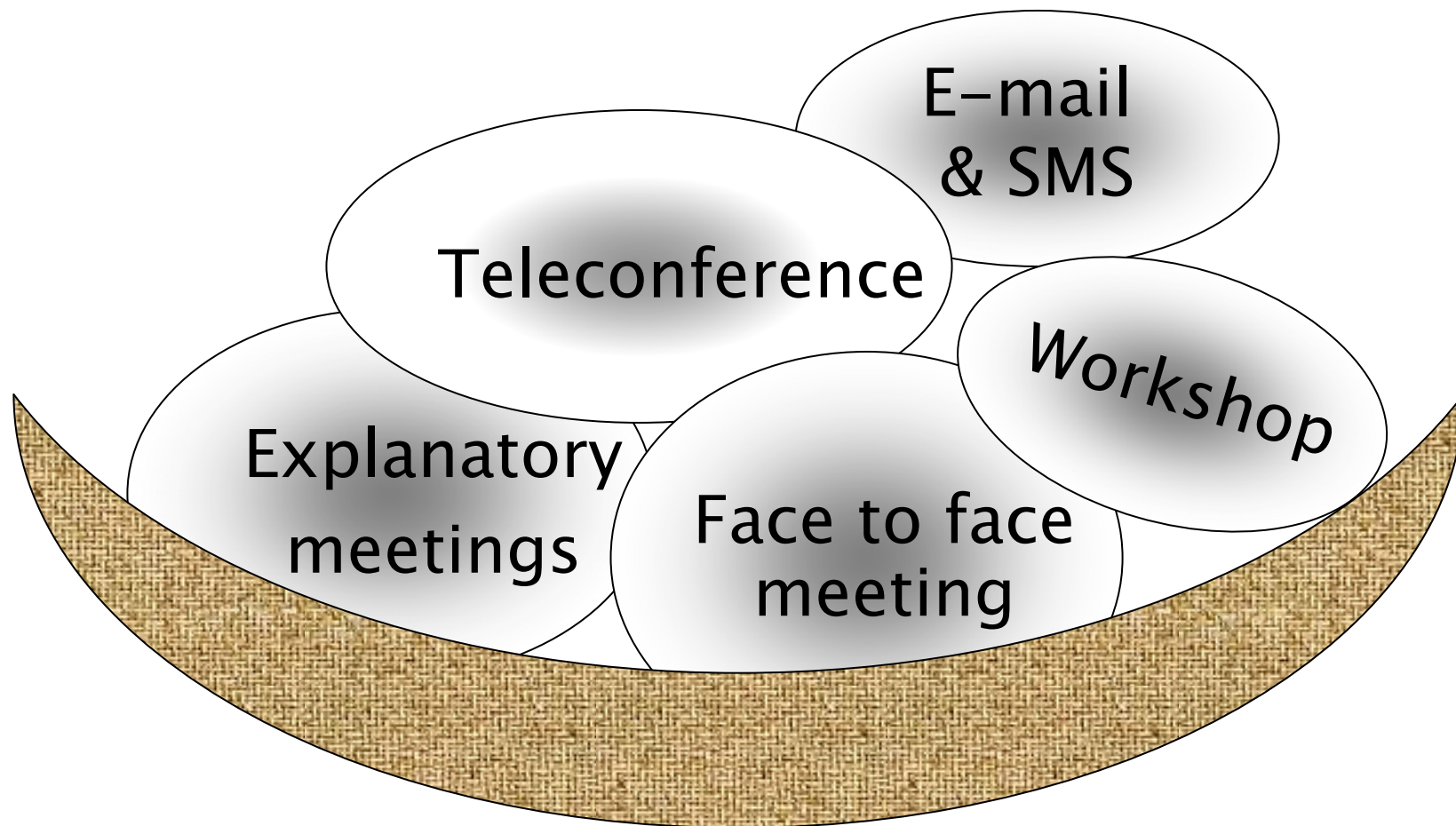
- After 2004.2.4., KFDA has engaged in the Good Review Practices
- Objective
 - Recognize that format influences content by imposing a logic to the review
 - Builds in quality by shaping both the conduct of the review and the presentation of the review results
 - Guarantee of quality, efficiency, clarity,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

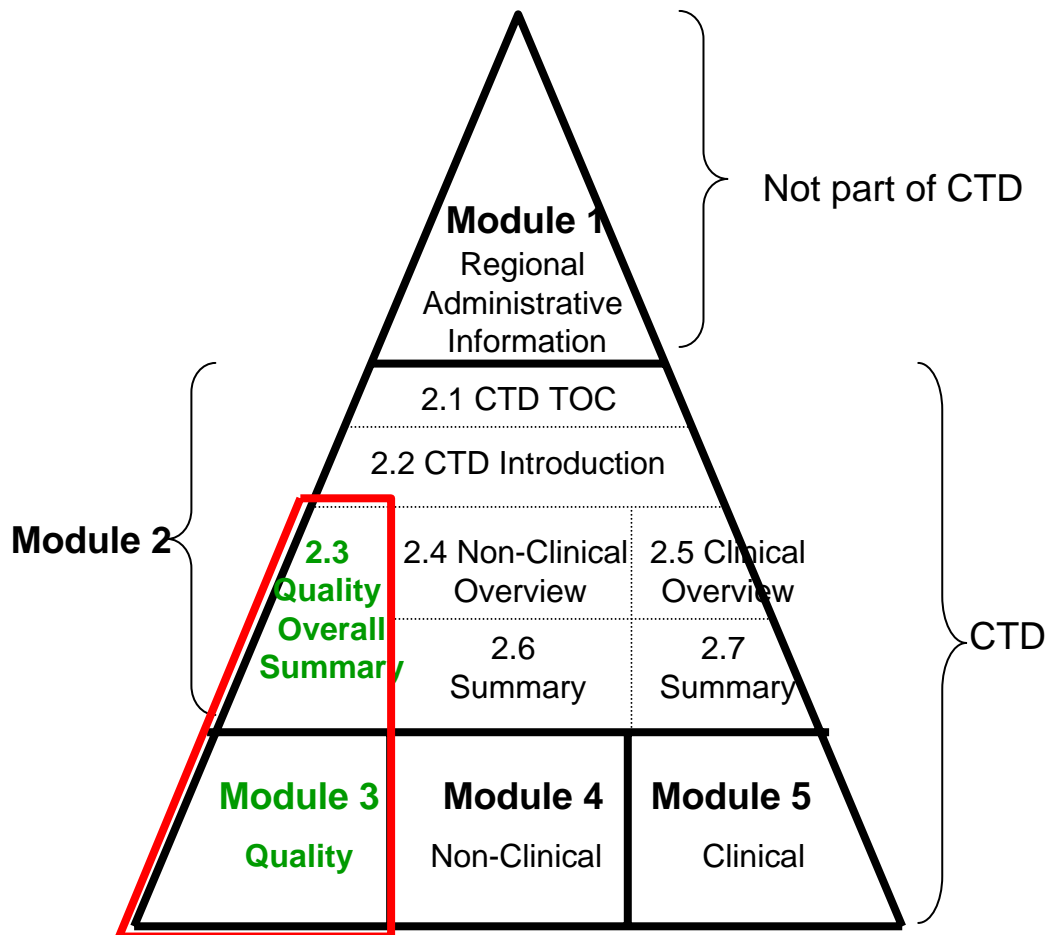
Dialogues between customers and the KFDA



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



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Drug Master File (DMF)

KDMF Introduction

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

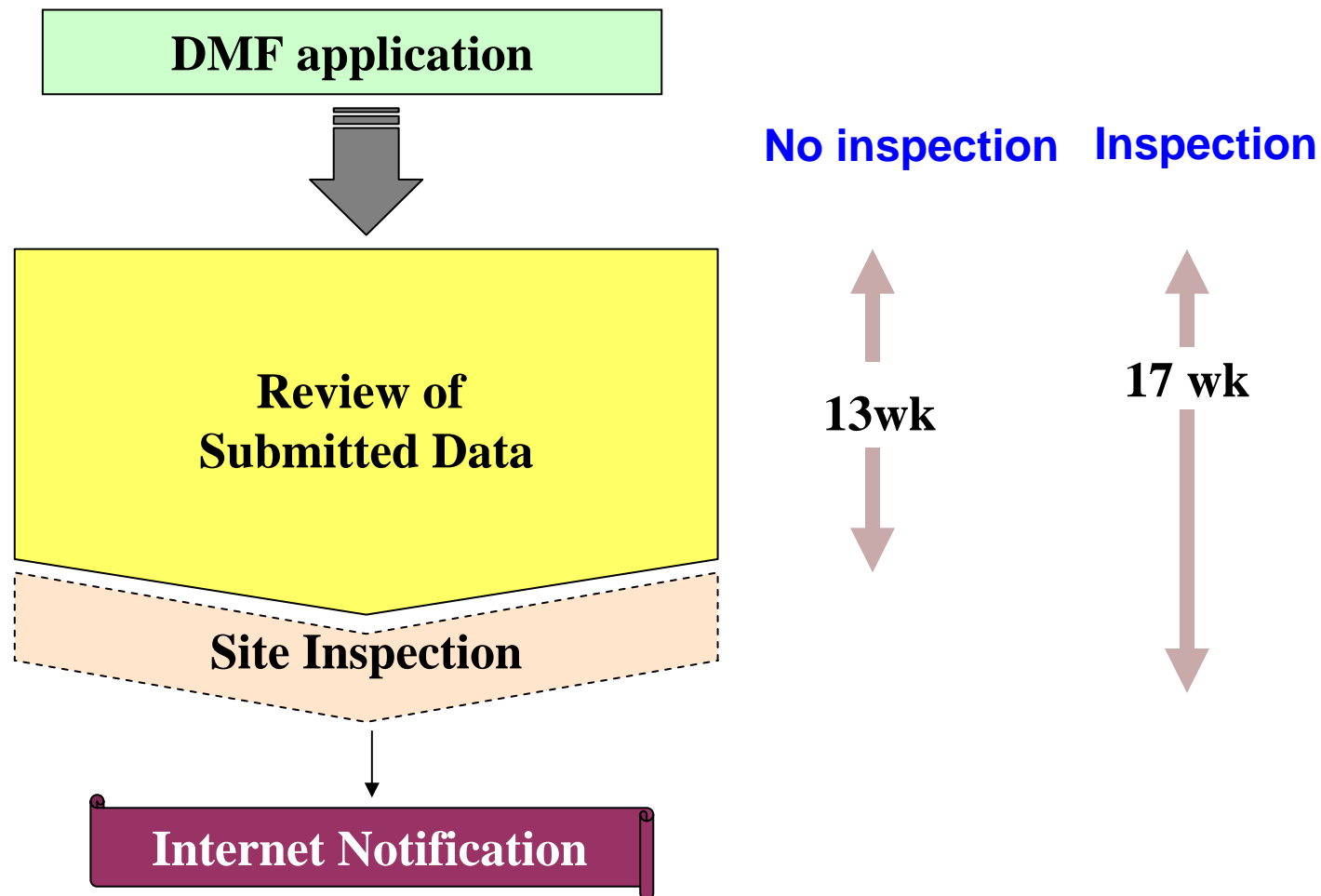
- **Background**
 - Concerns about using low quality of drug substances
 - Quality control of drug substances
- **Scope**
 - New chemical entities used as APIS
 - Phase-in of other APIs registration

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



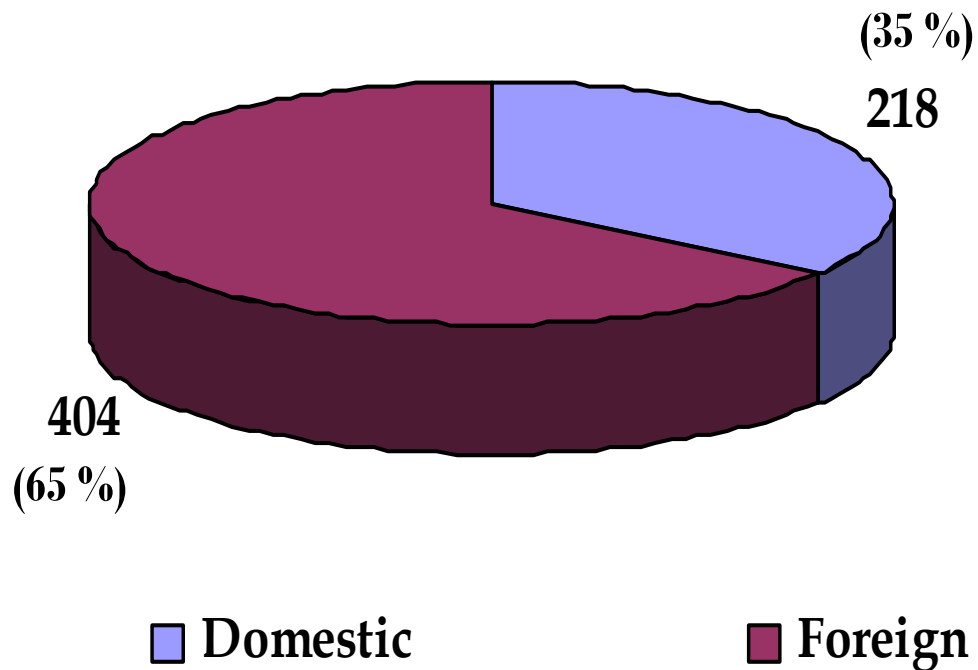
Data Requirements for DMF Review

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 →

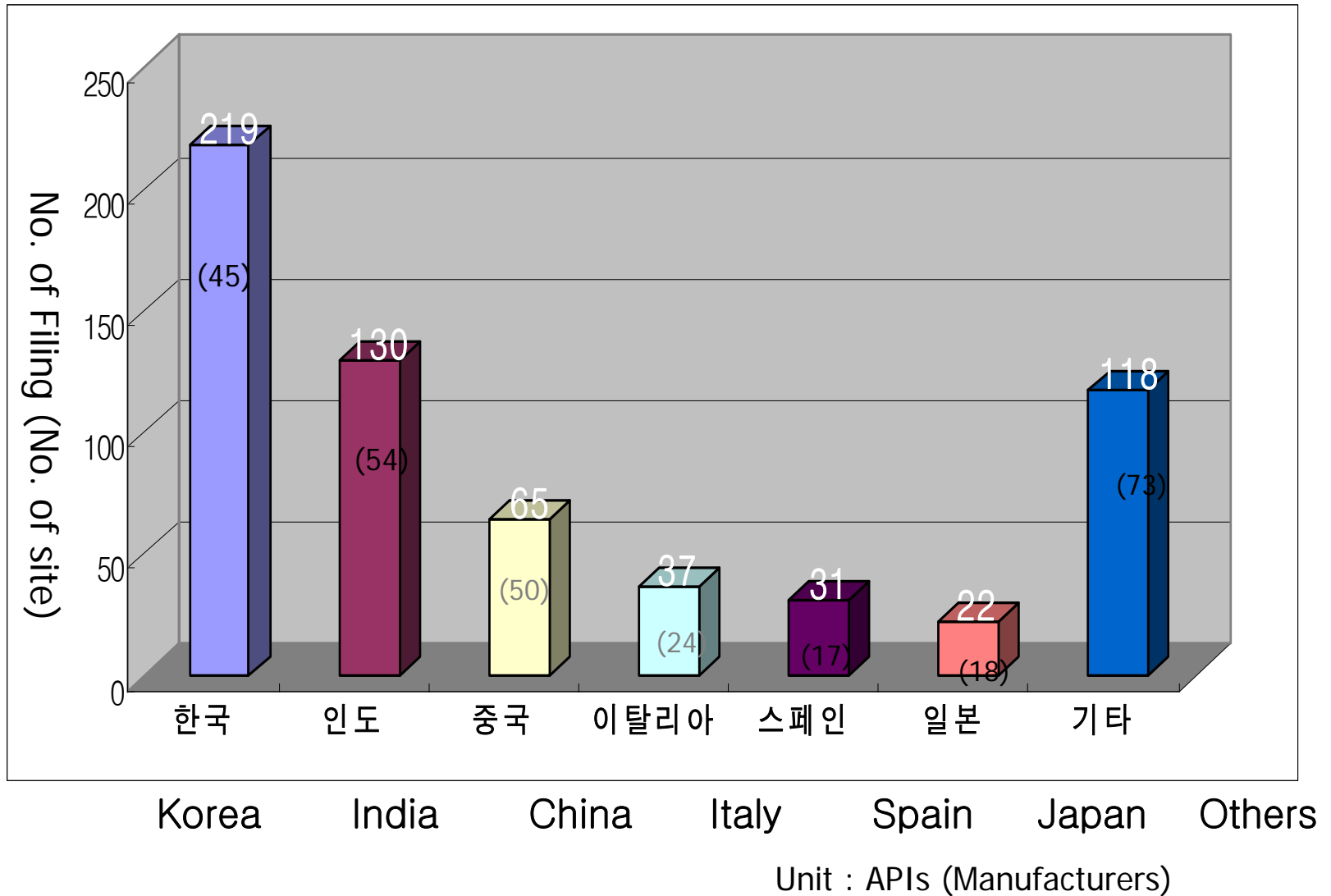


Ratio of APIs (Domestic vs Foreign)



77 APIs (Total 622 items)

77 APIs filed



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.*

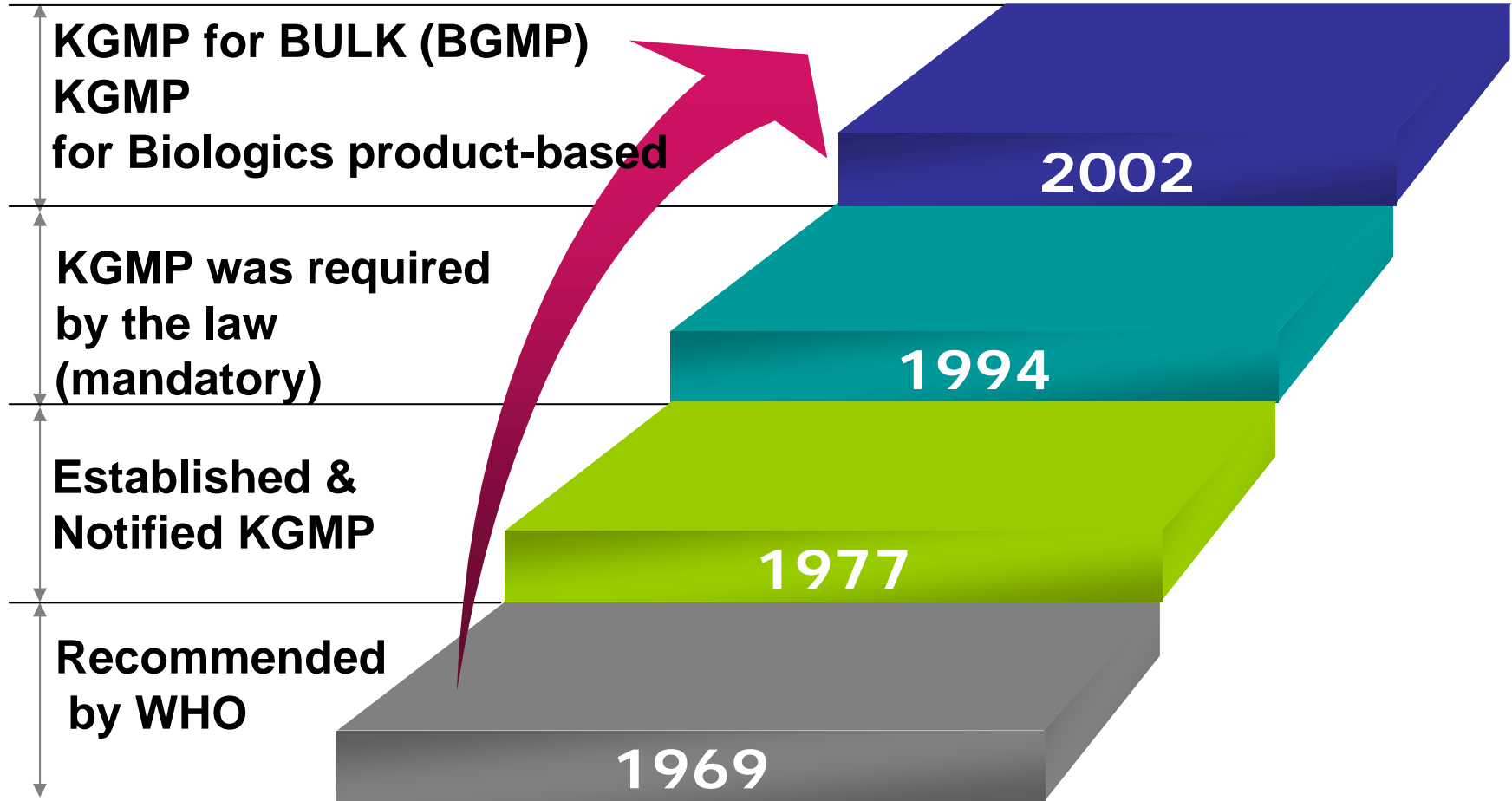


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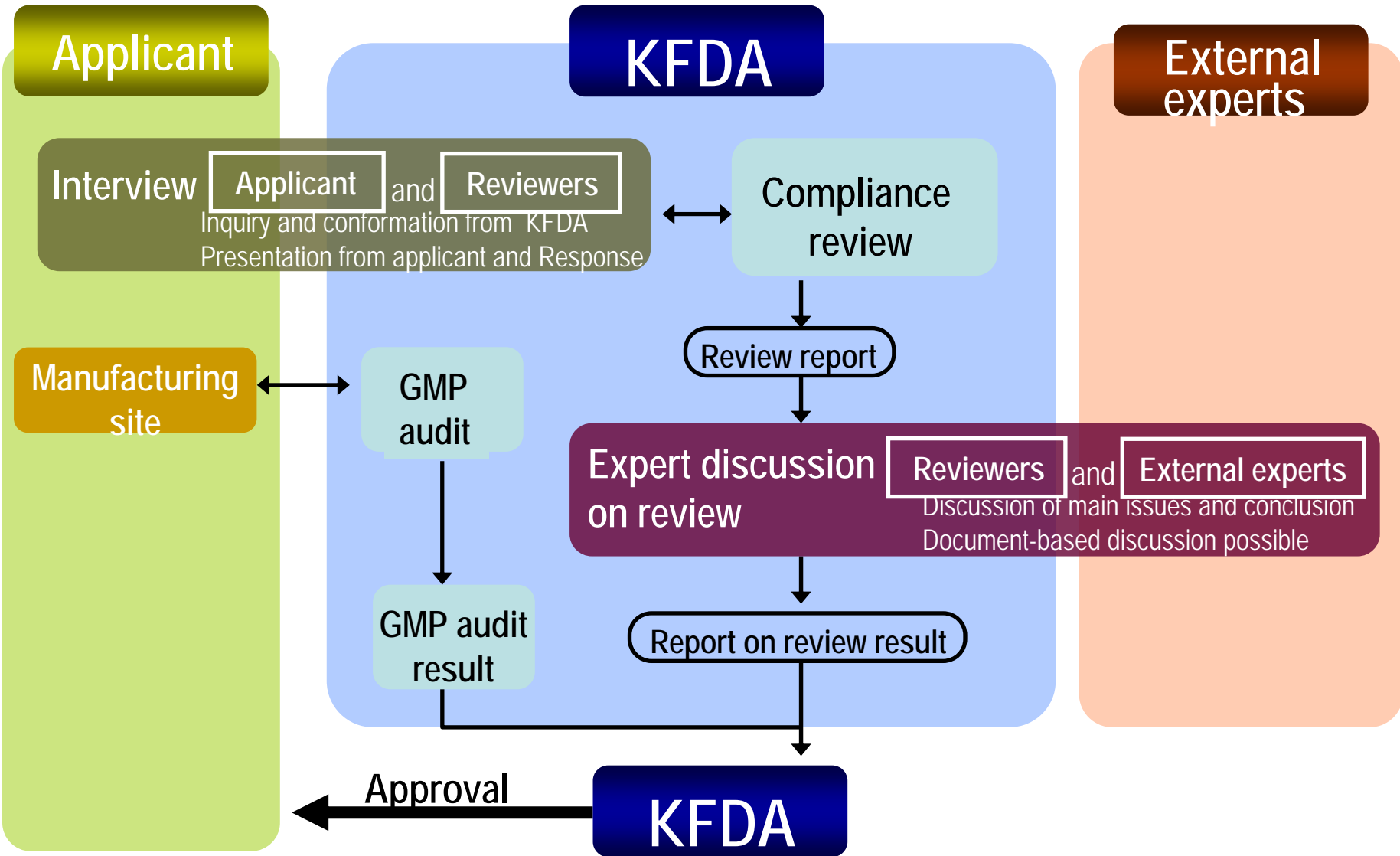


Good Manufacturing Practice (GMP)

Milestone of GMP in Korea



Flow Chart of GMP Approval in Korea



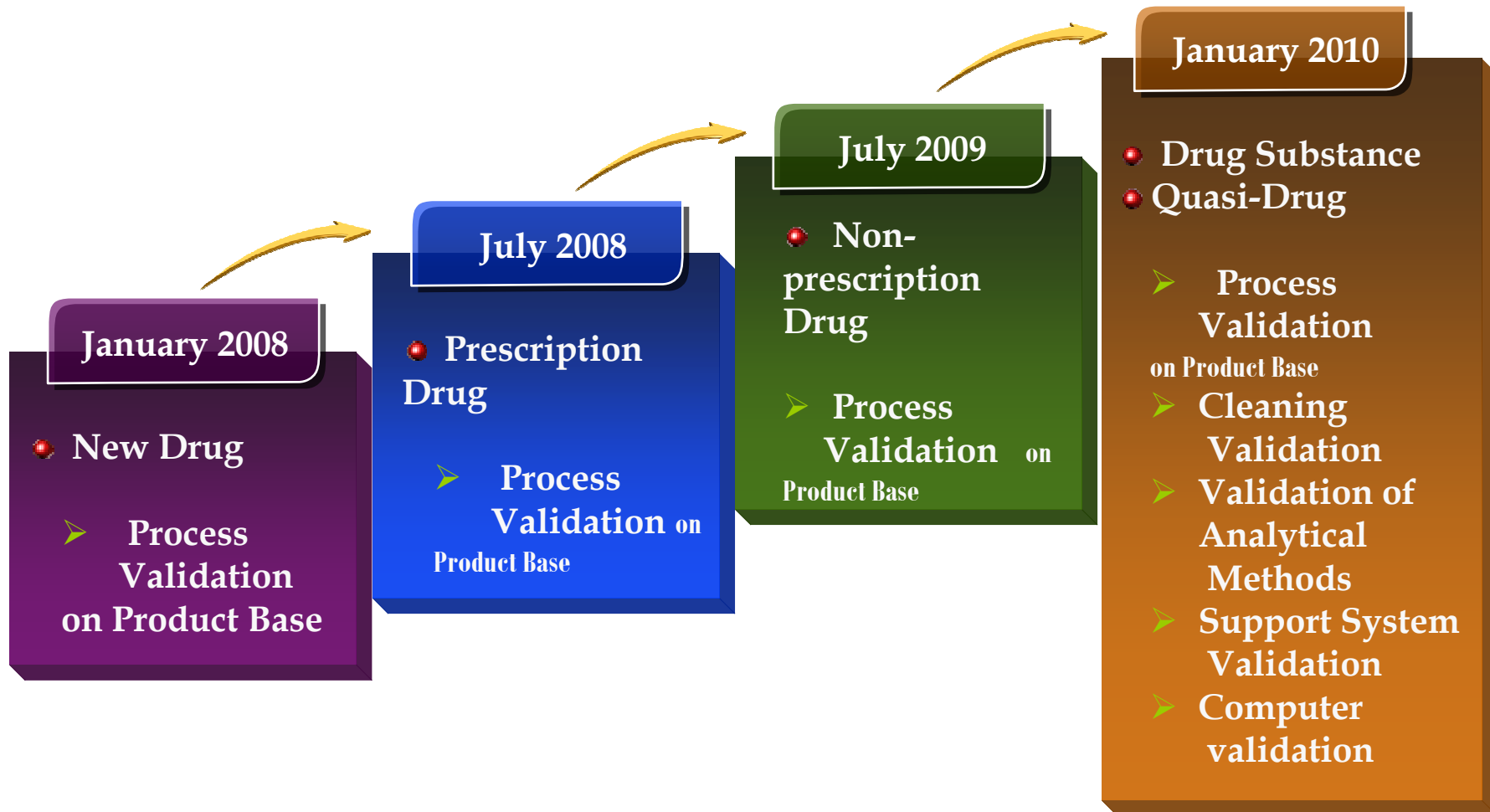
Current status

- 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



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Quality Control of Products on the Market

Annual Plan

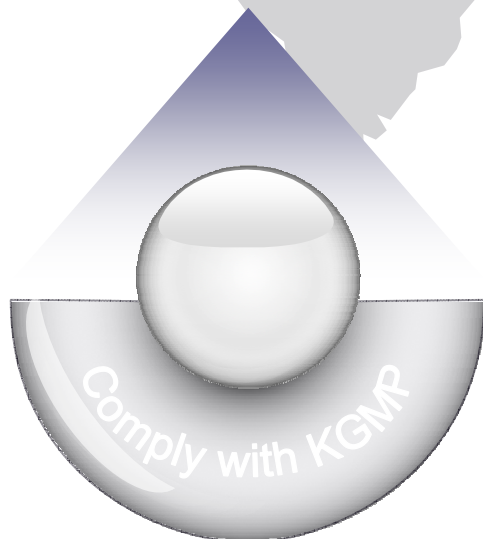
- Monitoring the quality of pharmaceutical products on the market
 - 2007 : 2,000 products
 - 2008 : 2,400 products
 - Pharmaceutical Bureau : 300 products
 - 6 Regional KFDAs : 2,100 products

International Harmonization

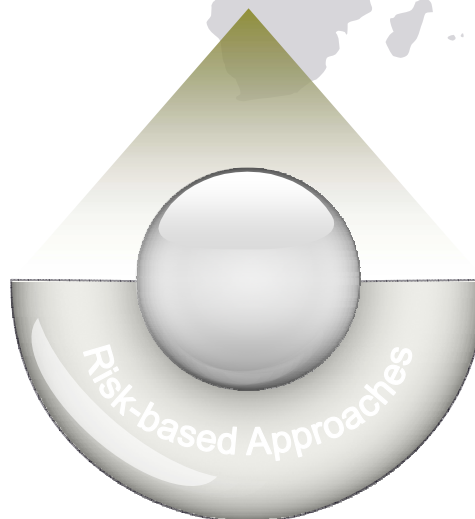
- **Japan-China-Korea Director-General Level Meeting 2008.4.14 Japan, Tokyo**
- **2008 East Asian Pharmaceutical Regulatory Symposium 2008.4.14-15 Tokyo, Japan**
- **13th ICDRA meeting in Switzerland, Bern 2008.9.16-21**
- **44th DIA Meeting in USA, Boston 2008.6.21-28**
- **US FDA's CDER Forum for International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

Internationally Harmonized Quality System

**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

| Vision |

정사어린어집

동물사육실험동

국립독성연구소

식품의약품안전청

중앙통제센터

질병관리본부

국립보건연구원

중앙후생관

한국보건산업진흥원

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Safe country for food and pharmaceutical product at the level of advanced countries which can obtain outstanding trust among the nationals

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Knowing the entire nation's hope for reliable safety management, KFDA has established 24 policy objectives in 4 major areas such as food / nutrition and functional food, pharmaceutical / biologics products, medical devices and toxicological research for the promise of a safer world.

Making a safe and reliable world where the entire nation can enjoy healthy lives is a long-cherished desire of all.

