GMP system in Japan and globalization efforts

Office director
Shingou Sakurai,PhD

Office of GMP/QMS Inspection
Pharmaceuticals and Medical Devices Agency (PMDA)

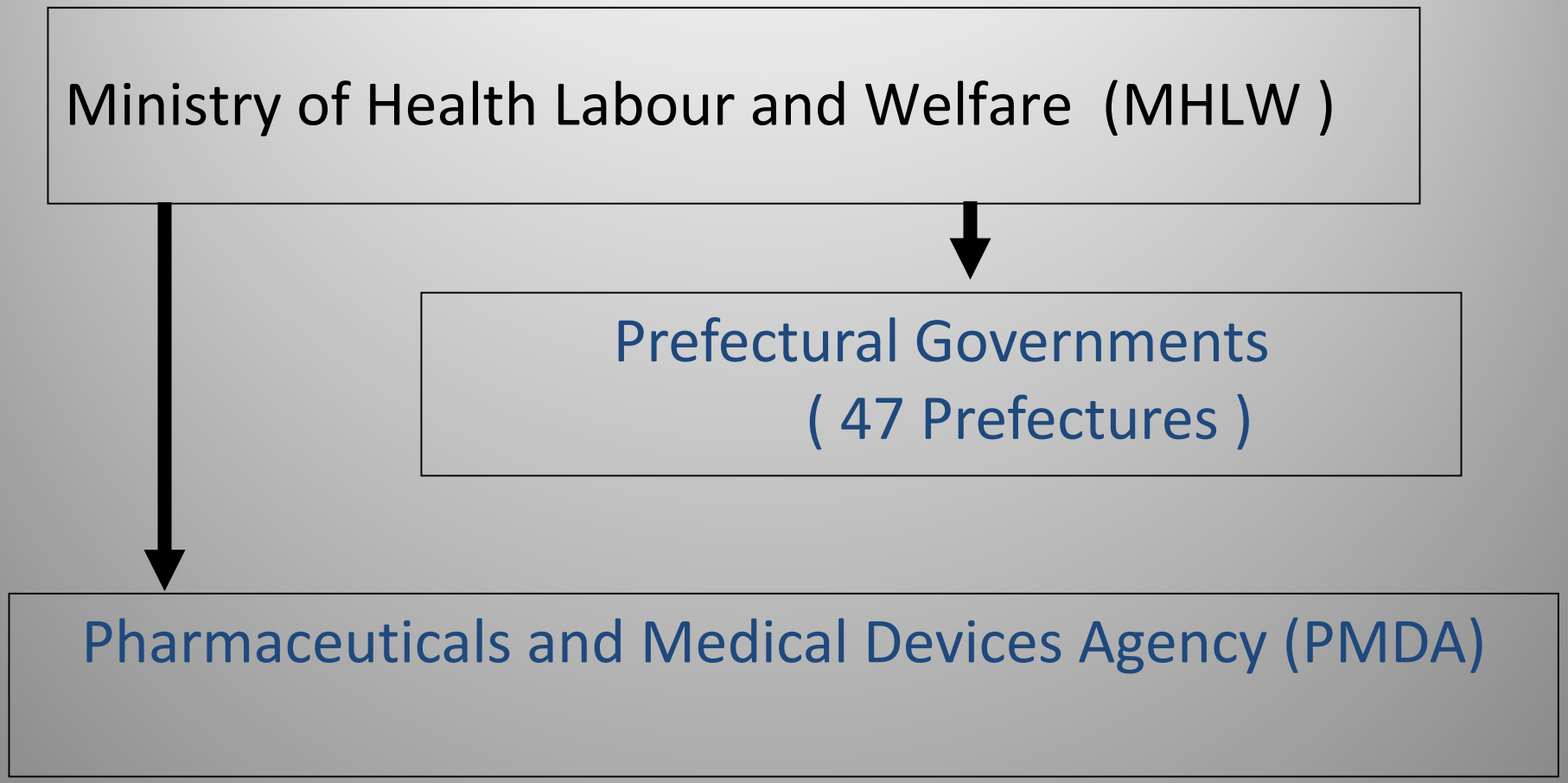
March 29, 2011

Topics

- ***Operations of the Office of GMP/QMS Inspection***
- ***The Revised Pharmaceutical Affairs Act and GMP inspection system***
- ***Overseas GMP inspections***
- ***Recent topics of globalization***
  1. ***ICH***
  2. ***Preparation for PIC/s accession***
  3. ***MRA between Japan and EU***

Operations of the Office of GMP/QMS Inspection

GMP Inspection Authorities in Japan



PMDA (established in April 2004)

Offices of General Affairs, Planning & Coordination

Adverse Health Effect Relief Services

Center for Product Evaluation

Office of Relief Funds

PMDA

Review

New Drugs, Medical Devices, Biologics, Generics and OTC

Audit *GLP and GCP*

Standards

JP secretariat

Office of GMP/QMS Inspection

Office of Safety

Inspection *GMP AND QMS*

Post-marketing safety

Reviews and related Operations

Office of GMP/QMS Inspection

Planning and Management Division

Administration and coordination

GMP Inspection

GMP Inspection of pharmaceuticals

QMS Inspection

QMS Inspection of medical devices and *In-vitro* diagnostics

PMDA GMP Inspection System

(As of March 2011)

Number of GMP inspectors : total 28

- **GMP experts: 9**
- **GMP inspectors (excl. office director): 19**

  with GMP experience at private companies: 7

  without GMP experience (new employees, etc.): 12

(* Members acting concurrently as reviewers

in the Office of Review 56)

Inspection authorities:
PMDA and Prefectural Government

	Domestic Site	Foreign Site
New drugs, Biological products, Radio pharmaceuticals	PMDA	PMDA
Other drugs	Pref. Gov.	PMDA

Number of sites to be inspected by PMDA

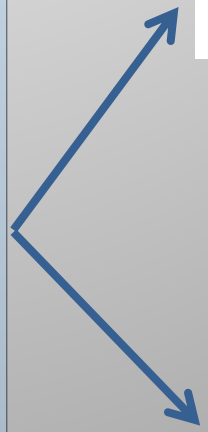
- Overseas manufacturing sites
  - ・Accreditated sites : 1796
    Asia, Middle East: 695
    Europe: 757
    North America, Latin America, Africa, Oceania : 344
  - ・Sites do not require accreditation
    (API intermediates, APIs made from food or other ingredients, etc) :
    : 283
- Domestic manufacturing sites
  - ・To be inspected by PMDA (Minister-licensed facilities):112
    Biological products, etc.: 95
    Radio-pharmaceutical product :17
  - ・New drugs, etc (sterile products to be authorized by prefectural governors, general products, etc.) : about 350

2 types of inspection methods
(On-site inspection / desktop inspection)

Risk analysis

Check points

- Information of manufacturing site
  (site history, country, areas of operation,
  dedicated/ shared equipment …etc.)
- New drugs or marketed products
- Dosage form (biological product, sterile product, tablet, ointment …etc.)
- Manufacturing process (aseptic process, cell culture, packaging only …etc.)
- Inspection history by foreign authorities (EU regulatory authorities, USFDA etc.)
- Inspection results by PMDA
  (previous on-site inspection result) etc.



Desktop Inspection

On-site Inspection

The Revised Pharmaceutical Affairs Act and GMP inspection system

Recent trends in pharmaceuticals and medical devices

- **Globalization**

  Globalization in product development, manufacture and distribution phases

  → Diversified corporate management strategy

- **Advanced technologies**

  Active ingredients, prescription, formulation development, process control, distribution control, etc.

  Biotechnology, genome, tissue engineering, etc.

  → Diversification of products and manufacturing process using cutting edge technologies

To provide safe and effective pharmaceuticals and medical devices to the patients,

To provide health benefit to the entire society,

Appropriate measures in accordance with the characteristics and risks of the products should be taken throughout the life cycle of the product.

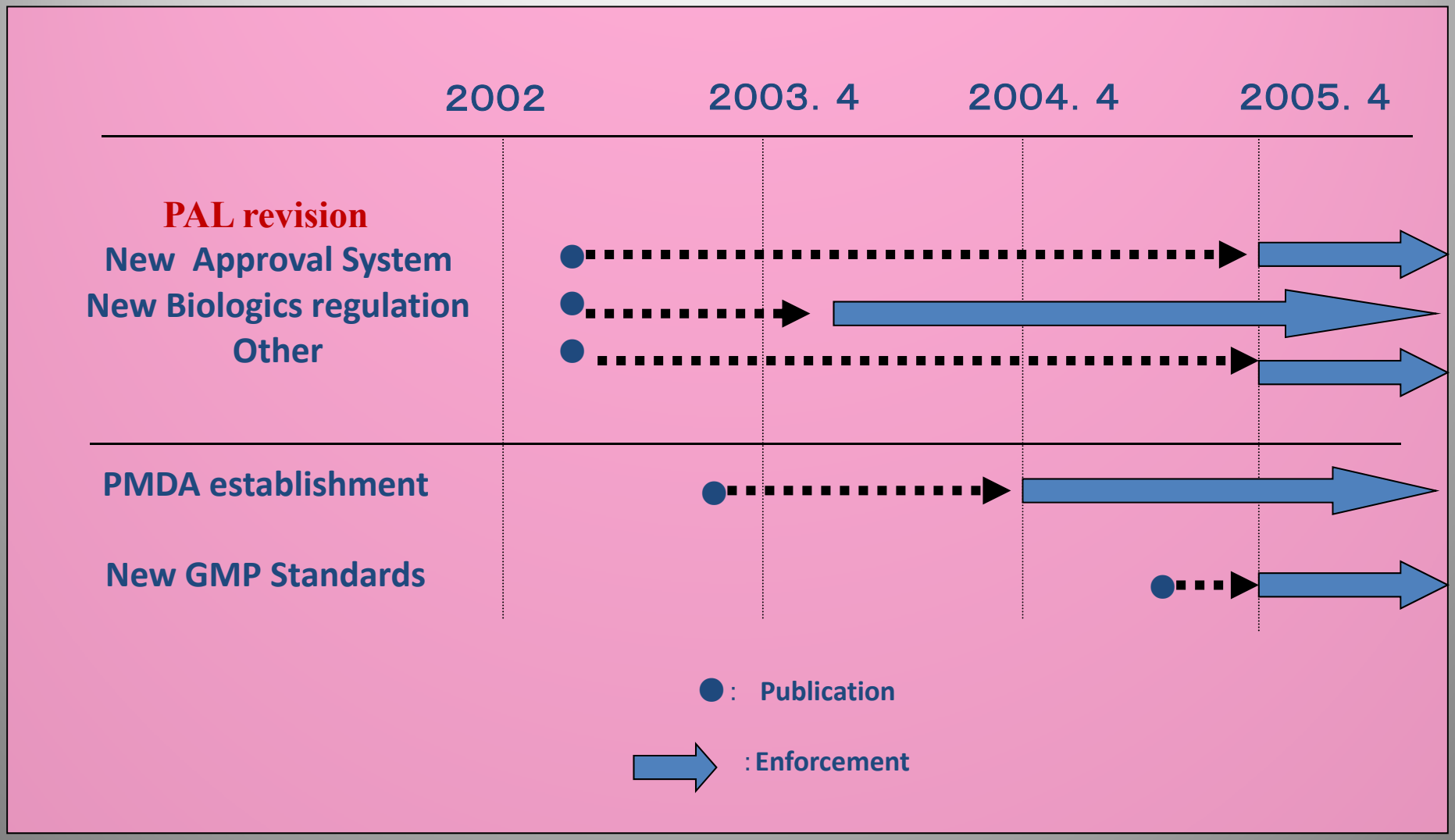
Global harmonization and cooperation has became more important.

Revised GMP system

- To meet the current needs of pharmaceutical and medical device industries in the 21 century,

GMP system was reorganized in 2002 as a drastic reform of pharmaceutical administration.

Enforcement of new regulations



The Revised Pharmaceutical Act. from quality perspectives

- **Overall**

1 Marketing and manufacturing, realization of consignment production
Quality management system based on the GQP

- **GMP inspection and authorization**

1 Introduction of GMP as requirement of marketing authorization,
GMP inspection for marketing authorization
2 Introduction of GMP as requirement of application for partial change of approved items
GMP inspection for authorization of partial change
3 Introduction of the accreditation system of foreign manufacturers and GMP inspection
4 Revision of GMP standard , introduction of change control and deviation control
5 Detailed description of manufacture-related items in the approval form
6 Introduction of master file system
7 Introduction of application of minor change in the approved items

- **Regulatory system**

1 Establishment of Pharmaceutical and Medical Devices Agency
2 Enhanced collaboration between review and post-marketing safety measures,
review and GMP inspection,
Post-marketing safety measures/Good Vigilance practice(GVP)
GMP/GQP

- **Others** Biological products

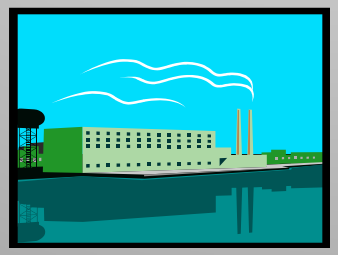
Responsibilities of MAH based on GQP

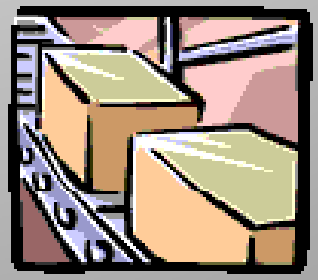
Total responsibility!

MAH

- Supervise and manage the manufacturers
- Ensure proper release to market

Manufacturer A (API) → **Manufacturer B (bulk product)** → **Manufacturer C (packaging, label)** → **Market Release**





GQP: Good Quality Practices

MAH: Marketing Authorization Holder

External Testing laboratory

GMP system in Japan

- GMP Ministerial Ordinance was issued as MHLW Ministerial Ordinance (Ordinance No. 179, 2004) and put into force in Apr. 2005.

http://www.pmda.go.jp/english/operations/pal/pdf/050909betsu2.pdf

Global Harmonization

- Introduction of change control, deviation control
- Responsibilities of quality assurance department
  (Quality assurance department needs to be independent from manufacturing department.)

Scope of Japanese GMP (1)

Manufacture of Drugs and Quasi-drugs

Contents

- Manufacturing control and quality control of APIs (comparable to ICH Q7)
- Dosage form
  - *-chemical and biological products*
  - *-radio-pharmaceuticals*
  - *-vaccines*
  - *-medicinal products derived from human blood and human plasma*
  - *-vitamins, minerals, herbal medicines*
- Foreign manufacturing sites (licensed as accredited* manufacturers)

*Requirement of foreign manufacturers' accreditation are equal to the domestic manufacturers' license (HR, Buildings & Facility)

Scope of Japanese GMP(2)

Manufacture of drugs and quasi-drugs

Does not include;

- pesticides and other biocides*
- disinfectants*
- hospital formularies
- medicinal gases
- powdering or cutting process of herbal crude medicines
- JP-listed excipients

*Limited to those which are NOT directly applied on human bodies

Inspection of Buildings and Equipment

“License” is for domestic manufacturers
“Accreditation” is for foreign manufacturers

Regulation: ‘Regulations for Buildings and Facilities of Pharmacies, etc.’
(MHLW Ministerial Ordinance No 2, 1961)

See our English web-site for the tentative translation.

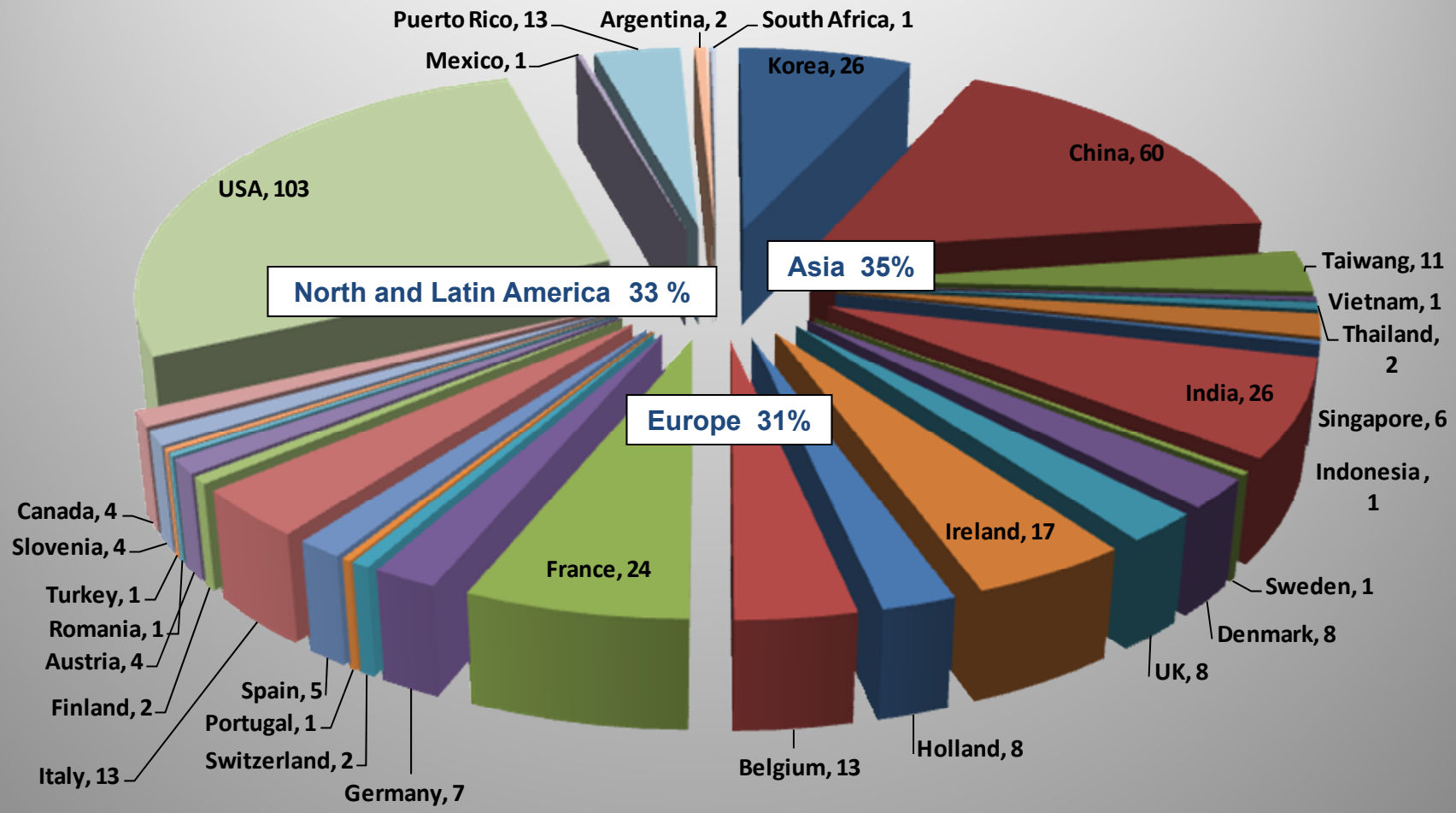
http://www.pmda.go.jp/english/operations/pal/pdf/050909betsu4.pdf

Overseas GMP inspection

How do we perform overseas Inspection?

- Same method as the domestic Inspections
- 2 Inspectors attended per inspection(in general)
- Accompanied by interpreters
- Duration : 3 to 4 days
- Notice: 3 – 6 weeks before the inspection
- Request for data submission prior to the inspection
- Focus on the points which were discussed among inspectors and determined based on the submitted data

Overseas inspections by country

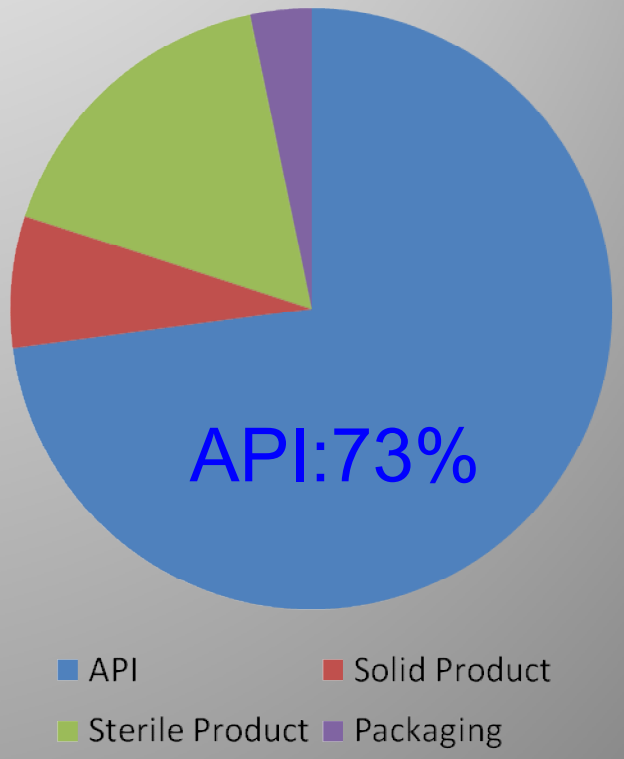


April 2005 ~ March 2011（376 sites and 31 countries)

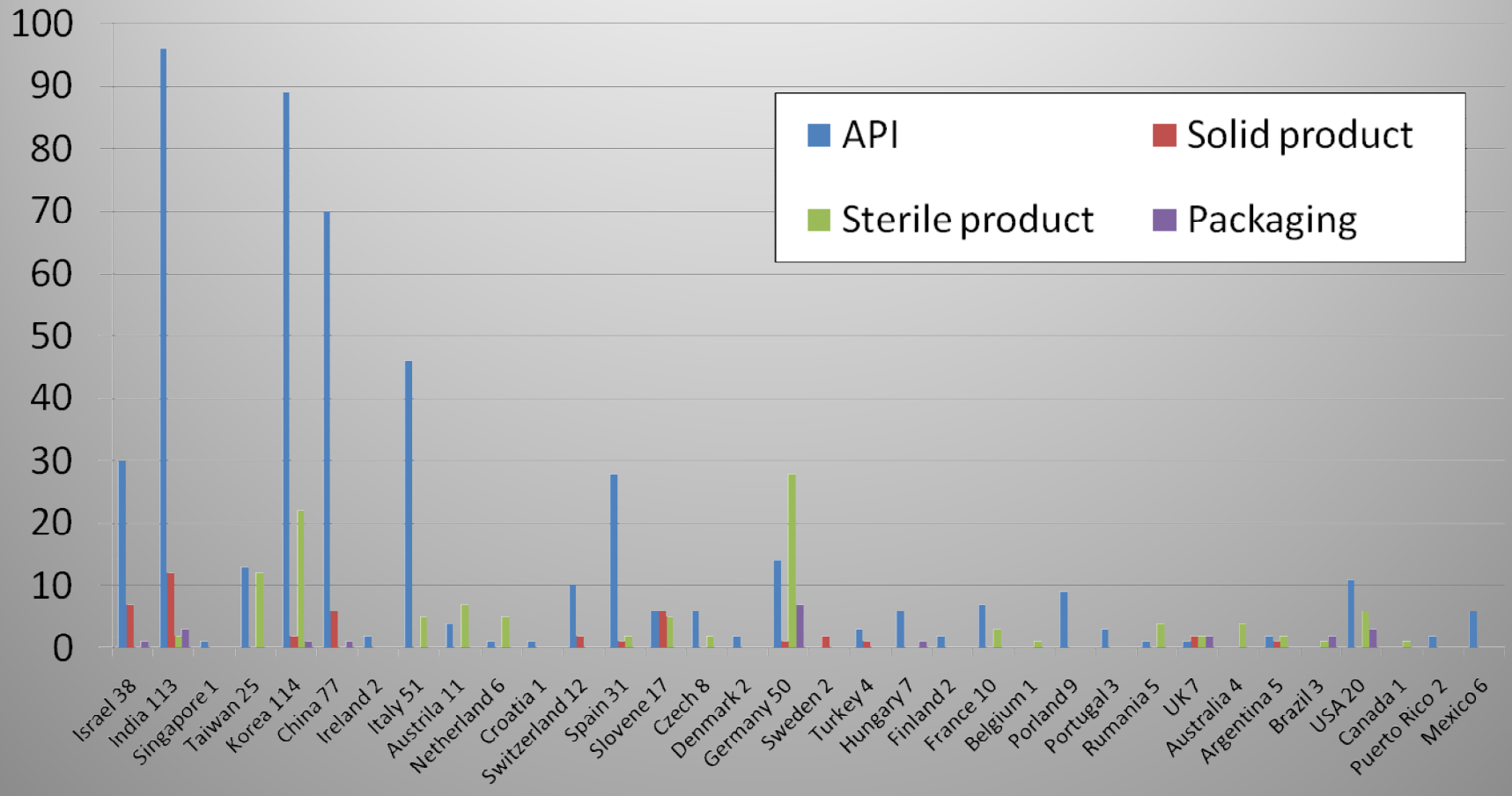
Summary of GMP inspections for generic products

(April, 2006 - March, 2011)

Category	EU	North America	Central and South America	Asia	Other	Total
Sterile drugs, Biological products	64	7	3	29	4	107
Solid products	15	0	0	30	0	45
API s (chemicals)	152	19	2	293	0	466
Packaging site, testing labs	10	3	2	6	0	21
Total	241	29	7	358	4	639



Summary of GMP inspections for generic products (Apr.2006-Mar.2011)



API: Korea, India, China Italy, ・・・・

To assure quality of imports from Asia

（Matters to be observed from GMP perspectives）

- Communication between manufacturers in Asia and Marketing Authorization Holders(MAHs) in Japan

  Notification system in cases of any changes in manufacturing methods or deviations
- Compliance to the Standard for Biological Ingredients

  Traceability of source materials, such as heparin
- Manufacturing/Quality control of Sterile products

  Environmental control, etc.
- Shared manufacturing area, facility and equipment with manufacturing of high pharmacological activities

  Containment, cleaning validation
- Quality control of Pharmaceutical Water

  Control items, action levels, etc.

Recent topics of globalization in GMP

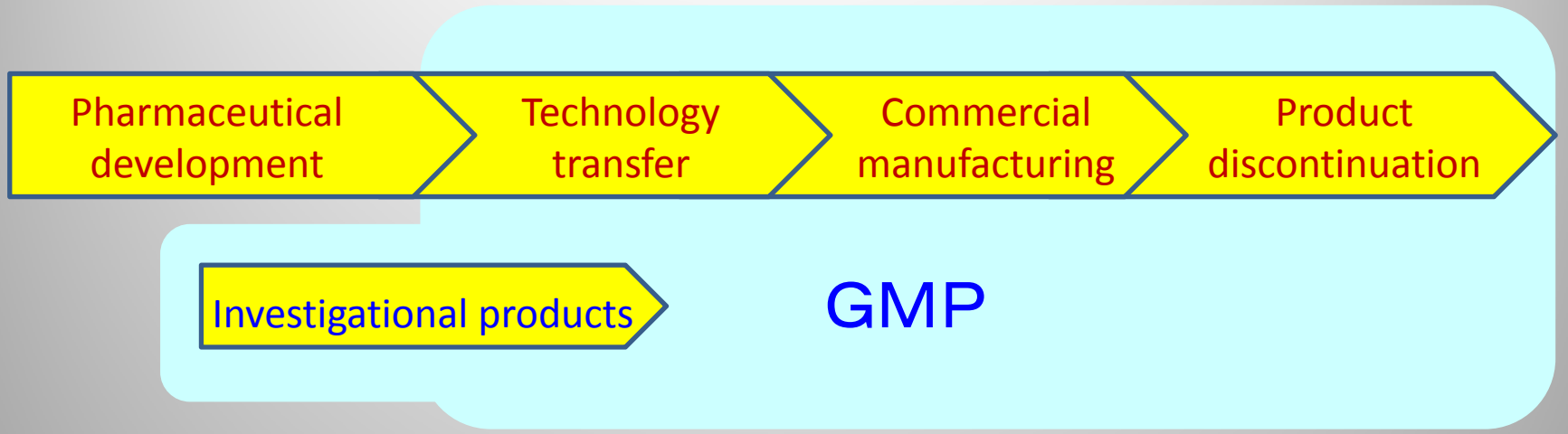
Recent topics of ICH
(GMP related matters)

Following quality guidelines were agreed .

* ICH Q8（Pharmaceutical development）
  - ICH Q8R2
* ICH Q9（Quality Risk Management ）
* ICH Q10（Pharmaceutical Quality System）

Those 3 guidelines are also known as “ICH Q trio”.

ICH Q10 Pharmaceutical Quality System



Management responsibilities

PQS element

Process performance & Product quality monitoring system
Corrective action and preventive action (CAPA system)
Change management system
Management review

Enablers

Knowledge management

Quality risk management

Guideline of pharmaceutical quality system
(February 19 2010, Notification from Director, MHLW)

ICH Q-IWG
Integrated Implementation Training Workshop

- Q-trio training workshops for assessors, GMP-inspectors and industry was hold in Europe US and Japan.
  - Training Workshop in Europe
    - Tallinn June 2-4, 2010
    - Cosponsored by PDA and ISPE
    - Participants (about 240 including approx. 100 regulators)
  - Training Workshop in US
    - Washington D.C. October 6-8, 2010
    - Cosponsored by PDA and ISPE
  - Training Workshop in Japan
    - Tokyo : October 25-27,2010
    - Cosponsored by PMRJ and JPMA
  - http://www.ich.org/cache/compo/276-254-1.html

PIC／S

Outline

PIC/S

Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
(Established in 1995)

Purpose

To develop and harmonize international GMP guidelines
To promote exchange of information and experience in the field of GMP
To facilitate the networking between participating authorities (mainly from Europe)

Accession

After application form is submitted, assessment will be undertaken to determine whether the pharmaceutical manufacturing system, quality standard, quality system of inspection, technical level of inspectors are comparable to those of other PIC/s participating authorities.

Current situation of PIC/s

- **Current PIC/s member countries : 39 (mainly from Europe)**
  This year, the US FDA was admitted to the membership.
- **Preparation for PIC/s accession is now under way in many countries.**
- **Participation of EMA and WHO as partners**

Benefit of PIC/s members

- **(Regulatory) Inspection resources will be saved by exchanging information among member countries.**
- **(Companies) Acceptance of inspection from PIC/s member countries will be omitted.**
- **(Pharmaceutical users)**
  Implementation of internationally harmonized GMP standard will ensure more secure and safe pharmaceutical usage.

Preparation for PIC/s accession

* Matters to be attended

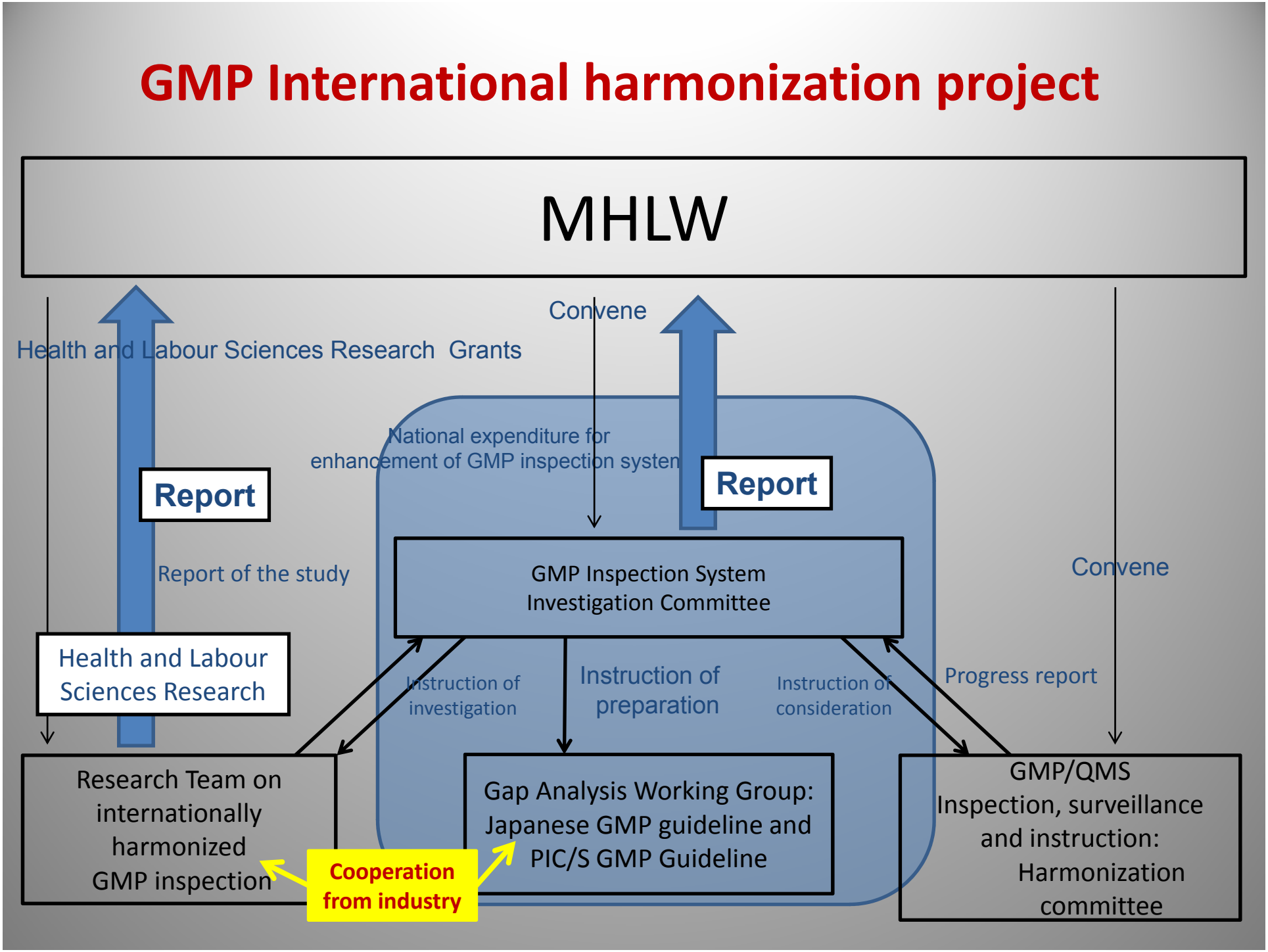
  1: Fill in a gap between PIC/s guideline and Japanese GMP guidelines

  2 : Review of quality system in PMDA and inspection departments in 47 prefectural governments

  3 : Improvement of technical skill of inspectors

An organization to ensure coordination among authorities in Japan will be established.

GMP International harmonization project



Mutual Recognition Agreement with EU

- Come into effect on May 29,2004
- Mutual Acceptance of GMP inspection results for manufacturing site and COA(certificate of analysis) for each batch of product
- Country: Belgium, Denmark, Germany, Greece, Spain, France, Ireland, Italy, Luxembourg, Netherlands, Austria, Portugal, Finland, Sweden, United Kingdom

International cooperation efforts

(1) Development of cooperation scheme among stakeholders (mutual benefit)

(2) Understanding of different GMP regulations in each country

(3) Training of Inspectors

(4) PIC/S accession

(5) Expansion of MRA scope between Japan and EU

(6) ICH, PIC/S, other activities

謝謝

Pharmaceuticals and Medical Devices Agency
(PMDA)
Office of GMP/QMS Inspection
TEL: +81-3-3506-9446
FAX: +81-3-3506-9465
web site; http://www.pmda.go.jp/

Finding GMP-related Information on PMDA Website

PMDA Office of Compliance and Standards

PMDA website in English

http://www.pmda.go.jp/english/index.html

Regulations and Procedures

PMDA, Office of Compliance and Standards

Accreditation of Foreign Manufacturers

Accreditation of Foreign Manufacturers

- Explanation of Application for Accreditation of Foreign Manufacturers (PDF)
- Category of Accreditation of Foreign Manufacturers (PDF)
- Examination Fees (PDF)
- List of Accredited Foreign Manufacturers (in Japanese)

GMP

PMDA , Office of Compliance and Standards

GMP

Announcement from Office of Compliance and Standards, PMDA

- Documents required by PMDA for the Application of GMP Compliance Inspection (PDF)
- [Form3] Outline of Drug Manufacturing Site (Foreign Manufacturing Site) (WORD)

Overview Guidance of GMP Compliance Inspection for Foreign Manufacturers

- GMP Compliance Inspection concerning Pharmaceuticals (including APIs) (PDF)
- Documents to be submitted for GMP Compliance Inspection (PDF)
- Important points for the industry Application for Periodic GMP Compliance Inspection (PDF)

Ministerial Ordinance on GMP

- Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs (Tentative Translation :as of September 9,2005) [GMP] (PDF)

Notifications

Notifications

Drugs

- Cancellation of items registered in Drug Master Files: PFSB/ELD Notification No.0208001, dated February 8, 2006 (PDF)
- Re: Q & A on use-results surveys conducted as All-Case Surveillance and Early Post-Marketing Phase Vigilance (EPPV) for Prescription Drugs: PFSB/ELD･SD Notice, dated September 7, 2009 (PDF)
- Basic Principles on Global Clinical Trials : PFSB/ELD Notification No.0928010 dated September 28, 2007 (PDF)
- Documents to Be Attached to Applications for Accreditation of Foreign Manufacturers of Drugs and Quasi-Drugs: PFSB/ELD Notification No. 1024002 dated October 24, 2005 (PDF)
- Guideline on Utilization of Master File for Drug Substances, etc. PFSB / ELD Notification No. 0210004 February 10, 2005 (PDF)
- Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law: PFSB / ELD Notification No.0210001 dated February 10, 2005 (PDF)
- Handling of Applications for GMP Inspections: PFSB/ELD Notification No. 0330006, PFSB/CND Notification No. 0330005, dated March 30, 2005 (PDF)

Ministerial Ordinances

PMDA , Office of Compliance and Standards

Ministerial Ordinances

Ministerial Ordinances

- Ministerial Ordinance on Standards for Quality Assurance for Drugs, Quasi-drugs, Cosmetics and Medical Devices (Tentative Translation :as of September 9,2005) [GQP] (PDF)
- Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs (Tentative Translation :as of September 9,2005) [GMP] (PDF)
- Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Medical Devices and In-vitro Diagnostic Reagents (Tentative Translation :as of September 9,2005) [QMS] (PDF)
- Regulations for Buildings and Facilities of Pharmacies, etc. (Tentative Translation :as of September 9,2005) (PDF)