Current GMP Inspection of PMDA

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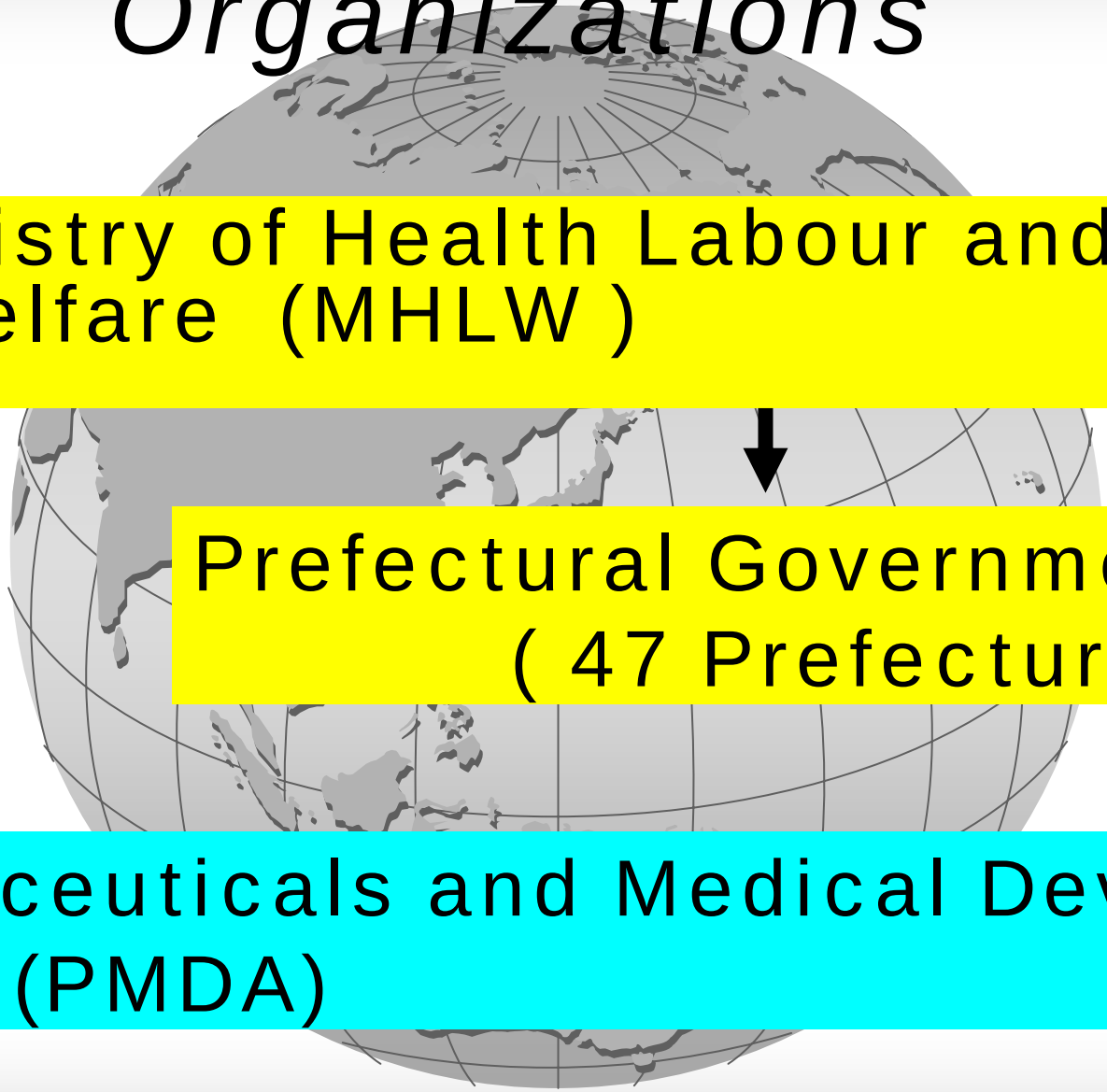
Pharmaceuticals and Medical Devices Agency（PMDA), JAPAN

GMP Inspection related Organizations in Japan

Organizations



Ministry of Health Labour and Welfare (MHLW)

Prefectural Governments (47 Prefectures)

Pharmaceuticals and Medical Devices Agency (PMDA)

Inspectors ~ Number ~

	Number	Remarks
MHLW	**57**	**P.I.**
Pref. Gov. (47)	**2,723**	**P.I.**
Designated Cities(60)/Wards(23)	**926**	**P.I.**
PMDA (1.Apr.2008)	**37**	**GMP/QMS (dedicated)**

Pharmaceutical Inspection (P.I.):

Not only GMP Inspection but also Inspection to Supervise or to Guide Poor Quality and/or incorrectly labeled (Advertised) Drugs (illegal drugs, counterfeit drugs, etc.)

GMP Inspecting Authorities in Japan

	Domestic Site	Foreign Site
New Drugs, Biological Products, Radio Pharmaceuticals	PMDA	PMDA
Other Drugs (General Drugs)	Pref. Gov.	PMDA

PMDA

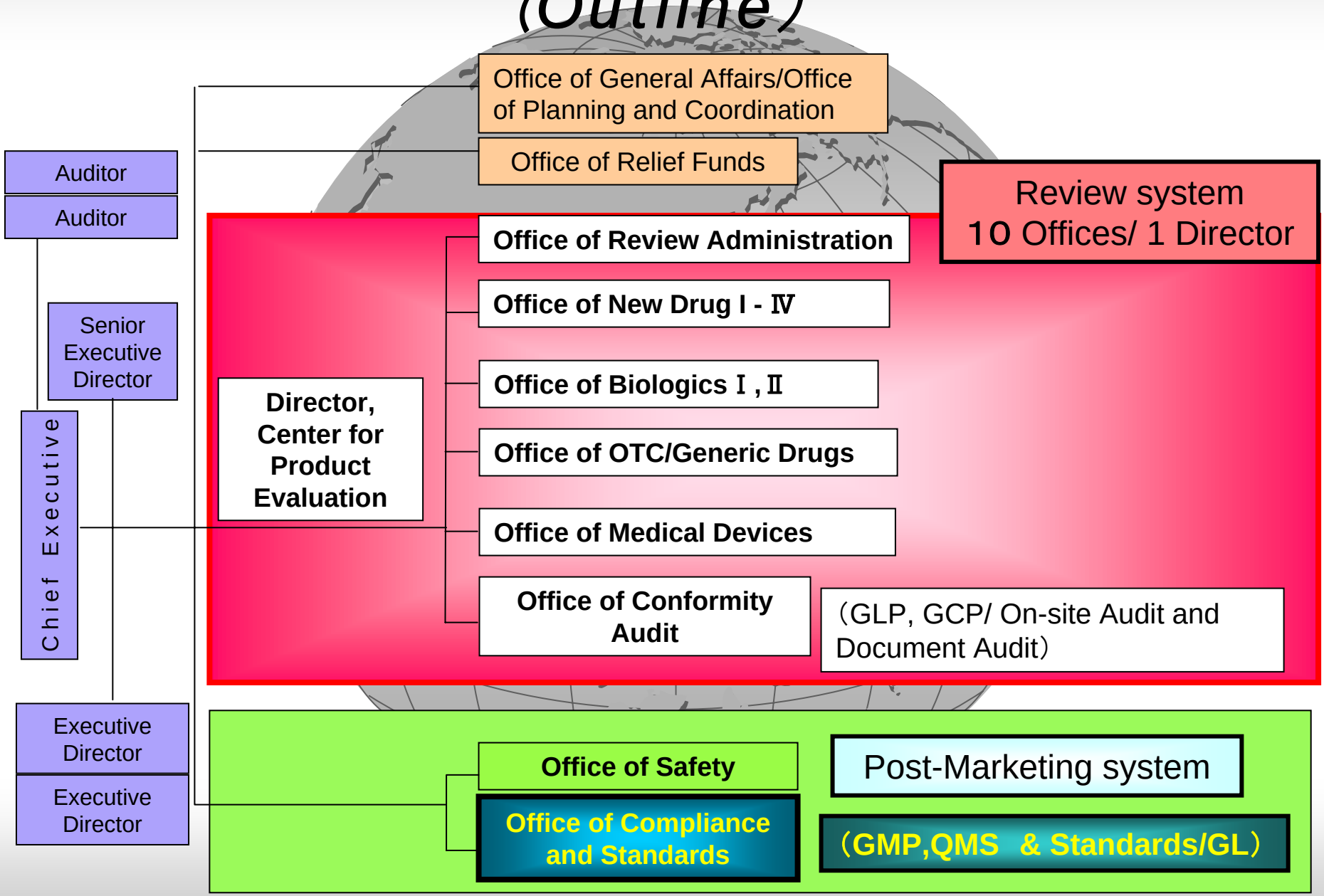
- Full Name: **Incorporated Administrative Agency – Pharmaceuticals and Medical Devices Agency**
- Abbreviation: **PMDA**
- Establishment: **April 1, 2004**
- Legal classification: **Incorporated administrative agency with non-civil servant status**

Our Mission

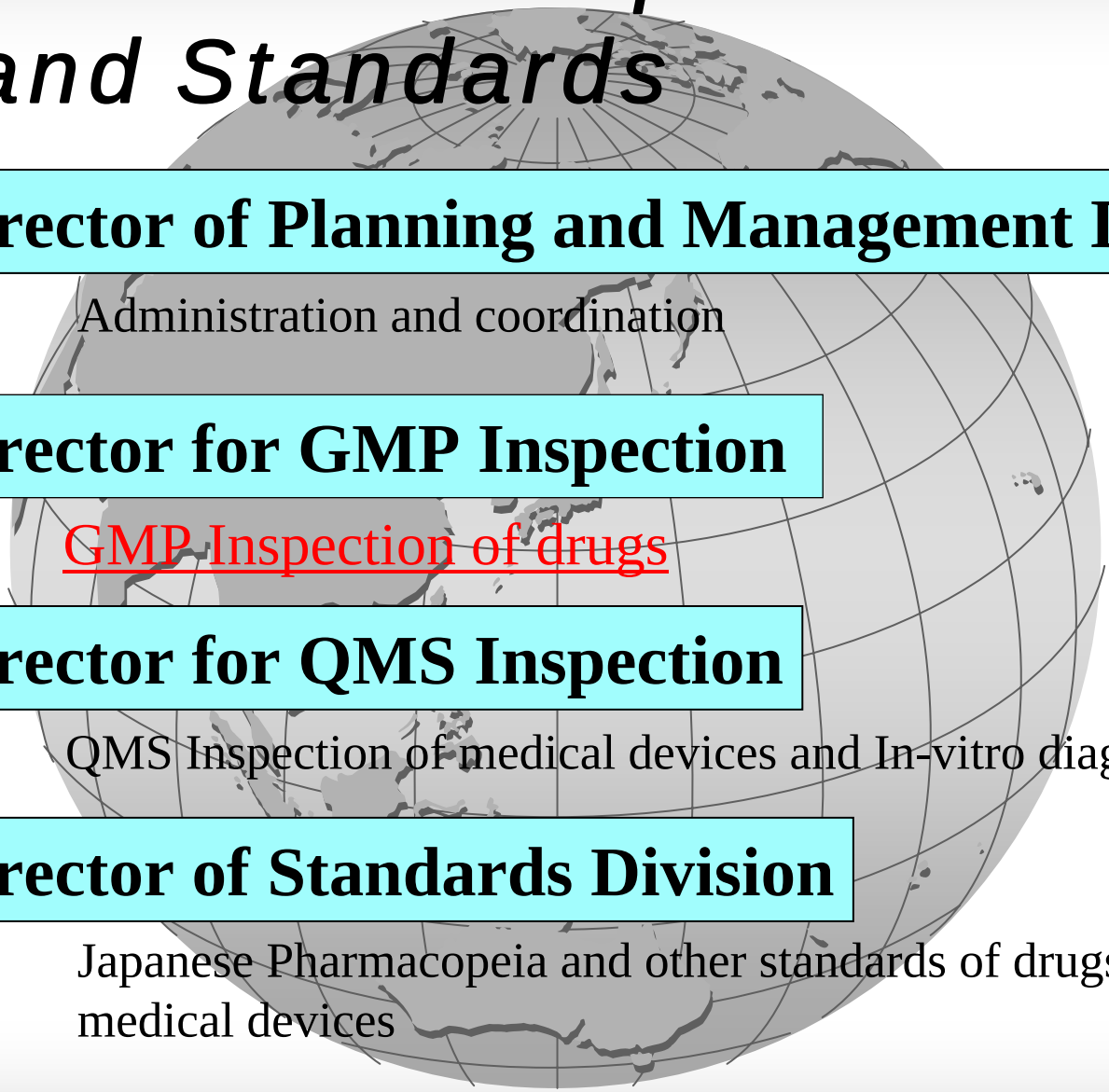
To ensure faster accessibility to better and safer drugs/devices for the public

Improving Public Health

PMDA Organizational Structure (Outline)



Office of Compliance and Standards



Office Director

Director of Planning and Management Division

Administration and coordination

Director for GMP Inspection

GMP Inspection of drugs

Director for QMS Inspection

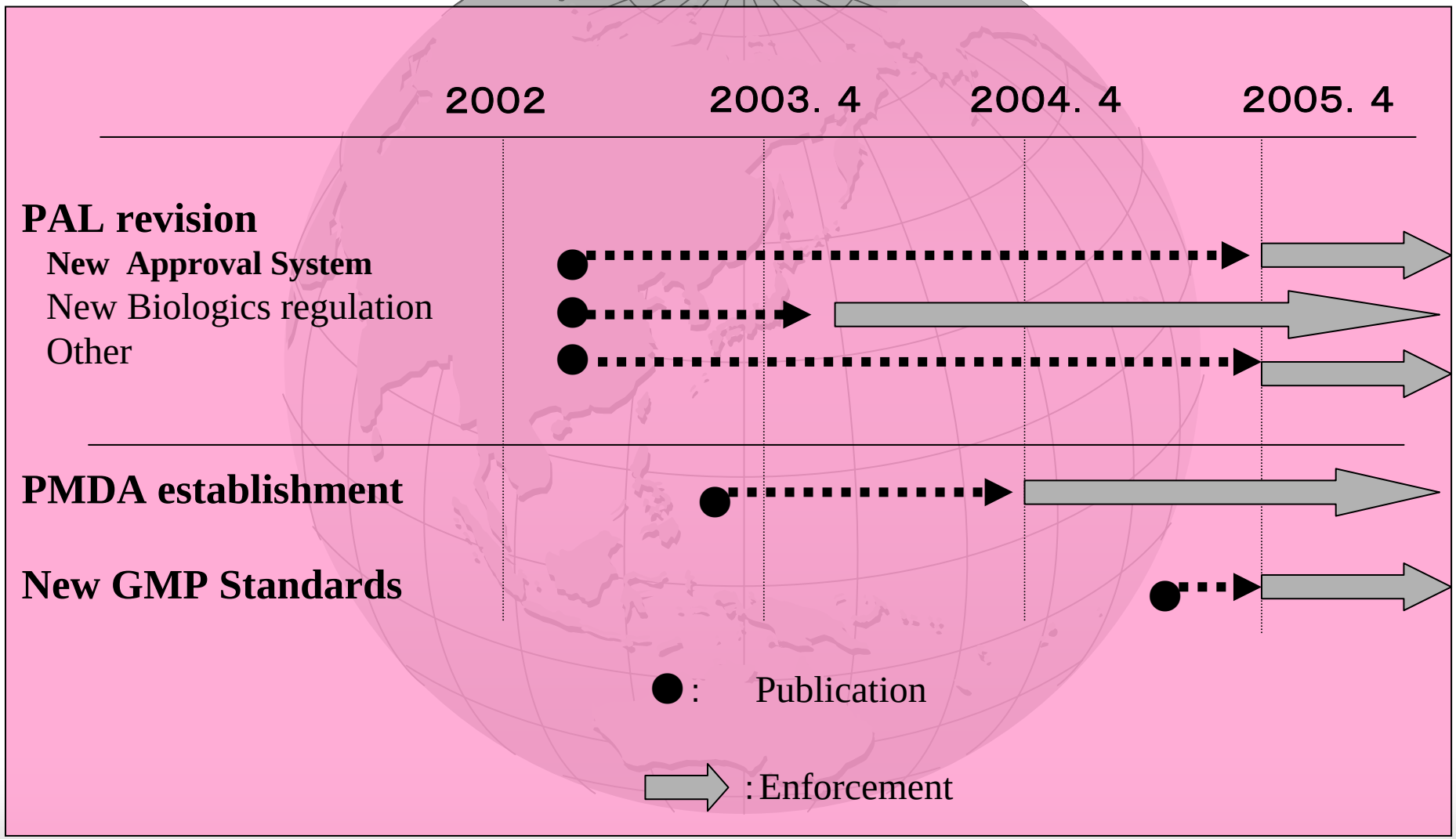
QMS Inspection of medical devices and In-vitro diagnostics

Director of Standards Division

Japanese Pharmacopeia and other standards of drugs and medical devices

Japanese GMP legislations

Enforcement of New Regulations



Approval System

Product Approval

Requirements
- **Quality, Efficacy & Safety of Products**
- **Licensed Stakeholder**
- **GMP-Compliant Manufacturing Sites**

Marketing Approval Application

Review & Inspection

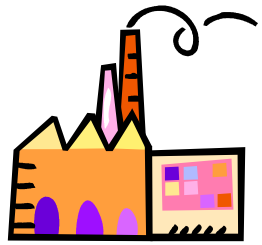
Marketing Approval

Release

License for Stakeholder

Drug Marketing License Holder (Product Distributor)

Licensed or Accreditated Manufacturer



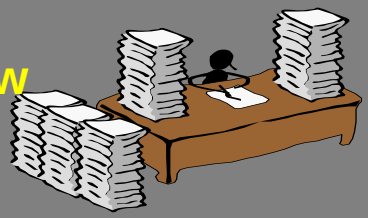
Requirements
- Human Resources
- GQP/GVP-Compliant

Requirements
- Human Resources
- Building & Facility

Review & Inspection

Application of New Drug

Review



New Drug

Application form

Submission

Pilot scale Data

Re-submission

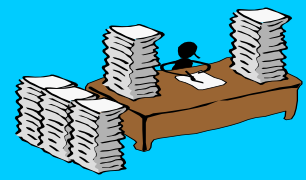
Production scale Data

Pre-Approval Inspection

Approval

Application of Partial Change (PC) of Approval

Review



Application of PC

Pre-Approval (PC) Inspection

Production Based on Approval

5-yearly Inspection

Requirement of license for manufacture or accreditation of foreign manufacturers

- **Regulation for Buildings and Facilities of Pharmacies, etc**

Requirement of product approval

Ministerial Ordinance on Standard for Manufacturing control and Quality Control for Drugs and Quasi-drugs (GMP)


Cherry Blossom at Mishima Shrine

GMP Inspections by PMDA

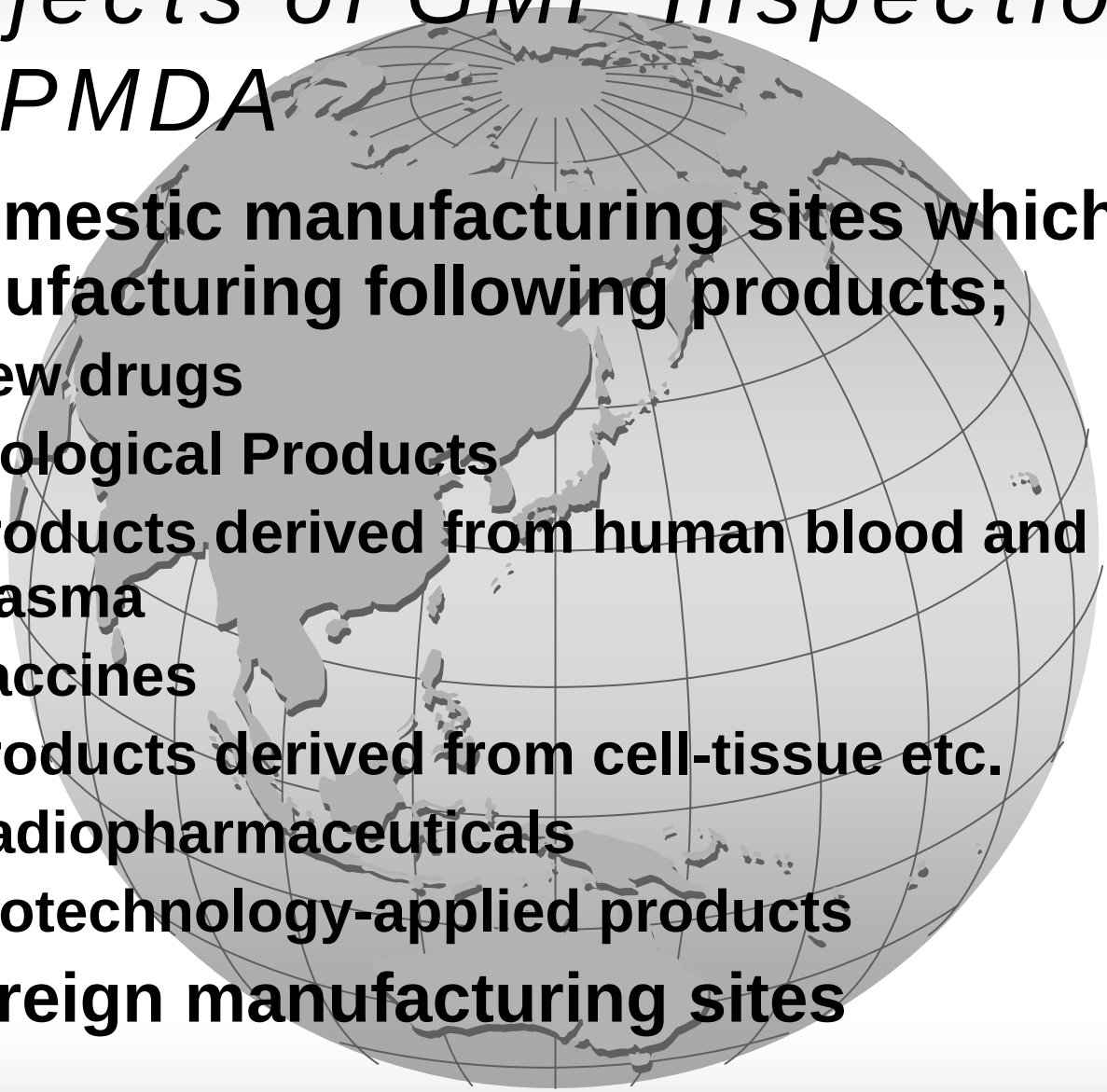
Types of GMP Inspection

- **Compliance Inspection**
  - **Pre-approval Inspection**
  - **Inspection conducted at the times of marketing approval renewal**
- **Inspection for license of minister permitted manufacturers**
- **Inspection for accreditation of foreign manufacturers**

(For cause inspection, Regular inspection)

- **On-site Inspections etc. (article 69-2)**
- **Cancellation etc. of Accreditation of Foreign Manufacturers (article 75-4)**

Subjects of GMP Inspection by PMDA



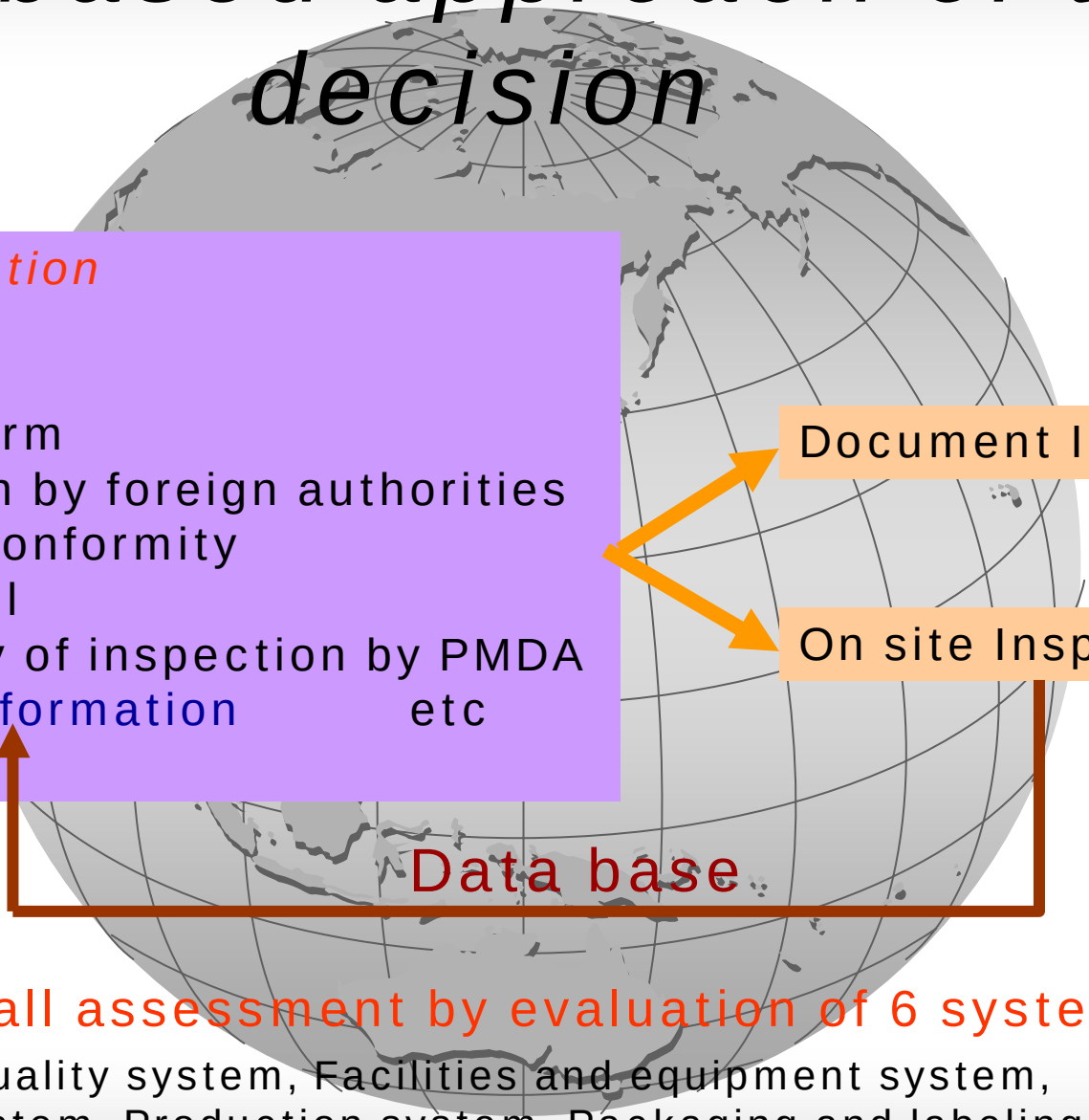
- **Domestic manufacturing sites which are manufacturing following products;**
  - **New drugs**
  - **Biological Products**
  - **Products derived from human blood and human plasma**
  - **Vaccines**
  - **Products derived from cell-tissue etc.**
  - **Radiopharmaceuticals**
  - **Biotechnology-applied products**
- **Foreign manufacturing sites**

Two types of GMP Inspection

- **On site Inspection**
- **Document Inspection**

Basically we conduct on site inspection, but select by risk based approach of some reasons for human resources

Risk based approach of the decision



Risk evaluation

- Product
- Process
- Dosage form
- Inspection by foreign authorities
- Past nonconformity
- Past recall
- No history of inspection by PMDA
- Facility information etc

Document Inspection

On site Inspection

Data base

Overall assessment by evaluation of 6 systems*

6 systems: Quality system, Facilities and equipment system, Materials system, Production system, Packaging and labeling system, Laboratory control system

Inspection schedule (standard)

Day 1:Morning

1. Opening meeting
2. Company and site overview (presentation by manufacturer)
3. Plant tour（1）
   - Warehouse

Day 1:Afternoon

- Manufacturing area, packaging area, in-process laboratory
- Support system
  - Water system
  - Air handling system
  - Waste treatment system

4. Plant tour（2）
   - QC laboratory
     - sample receiving area
     - testing area
     - biological tests
     - stability test area
     - retain sample area

Inspection schedule (cont.)

Day 2: Morning

5. Document check（1）

（1）Quality system

- **GMP organization, job description of key personnel**
- **Document control**
- **Standard cords, SOPs**
  - **Manufacturing control**
  - **Quality control**
  - **Manufacturing hygiene control**
  - **Product master file**

Day 2:Afternoon

- **Handling of Information on Quality, etc.**
- **Recall**
- **Deviation control**
- **Change control**
- **Training**
- **Release procedure**
- **Self inspection**
- **Control of contract manufacture, supplier control**
- **Written agreement with the Japanese marketing authorization holder**

Inspection schedule (cont.)

Day 3:Morning

6. Document check（2）
（2）Buildings and facilities
・Daily check of buildings, equipment and utilities
・Preventative maintenance

(3)Control of raw materials, packaging materials
・Material receipt, quarantine
・Sampling procedure, storage of released material, use for manufacture
・Compliance to the Japanese standard for the raw materials of animal origin

Day 3:Afternoon

（4）Manufacture
・Product standard code (Master formula) manufacturing instruction, batch record
・Validation
・Reprocess, rework
（5）Packaging and labeling
（6）Test and inspection

7. Summary by inspectors
8. Closing meeting
・Comments by inspectors
・Discussion

Follow up of the inspection

Written observation items (in Japanese) will be sent to the manufacturer (usually via marketing authorization holder) around 3 weeks after completion of inspection.

Written response (in Japanese) is required within 3 weeks.

Follow up of the inspection (cont.)

We request following points to prepare written responses to the observation items.

1. **Submit photographs or drawings if it is easy to demonstrate the corrective action.**
2. **Submit summary report if some tests or validation work are carried out.**
3. **If SOPs are revised, submit a copy of the revised part.**
4. **If completion of the corrective action is anticipated to take a time, submit a schedule of the action specifying the actions to be taken and expected time of report.**

Requests for document inspection

1. Outline of the manufacturing site
2. Site map, floor plan of the area involved in the manufacture and control of the product.

   (1) floor plan showing materials and personnel flow

   (2) floor plan showing level of environmental control in each area (room)

   (3) floor plan showing pressure difference

Requests for document inspection (cont.)

3. GMP organization chart and the document describing the quality assurance system
4. GMP document system
5. Manufacturing flow chart and detailed description of the actual manufacturing process of the product in the site
6. In-process controls and their limits for the product

(The documents related to the items 5 and 6 are master batch instruction, master batch record or manufacturing SOPs actually used in the site)

Requests for document inspection (cont.)

7.Documents for specifications and test methods for in-process material and finished product

8. Documents for specifications and test methods applied for the actual acceptance test of the raw materials described in the column of components and composition in the new drug application

(The documents related to the above items 7 and 8 are copies of product master file, master test and inspection record, or test and inspection procedure of the relevant raw materials actually used in the site)

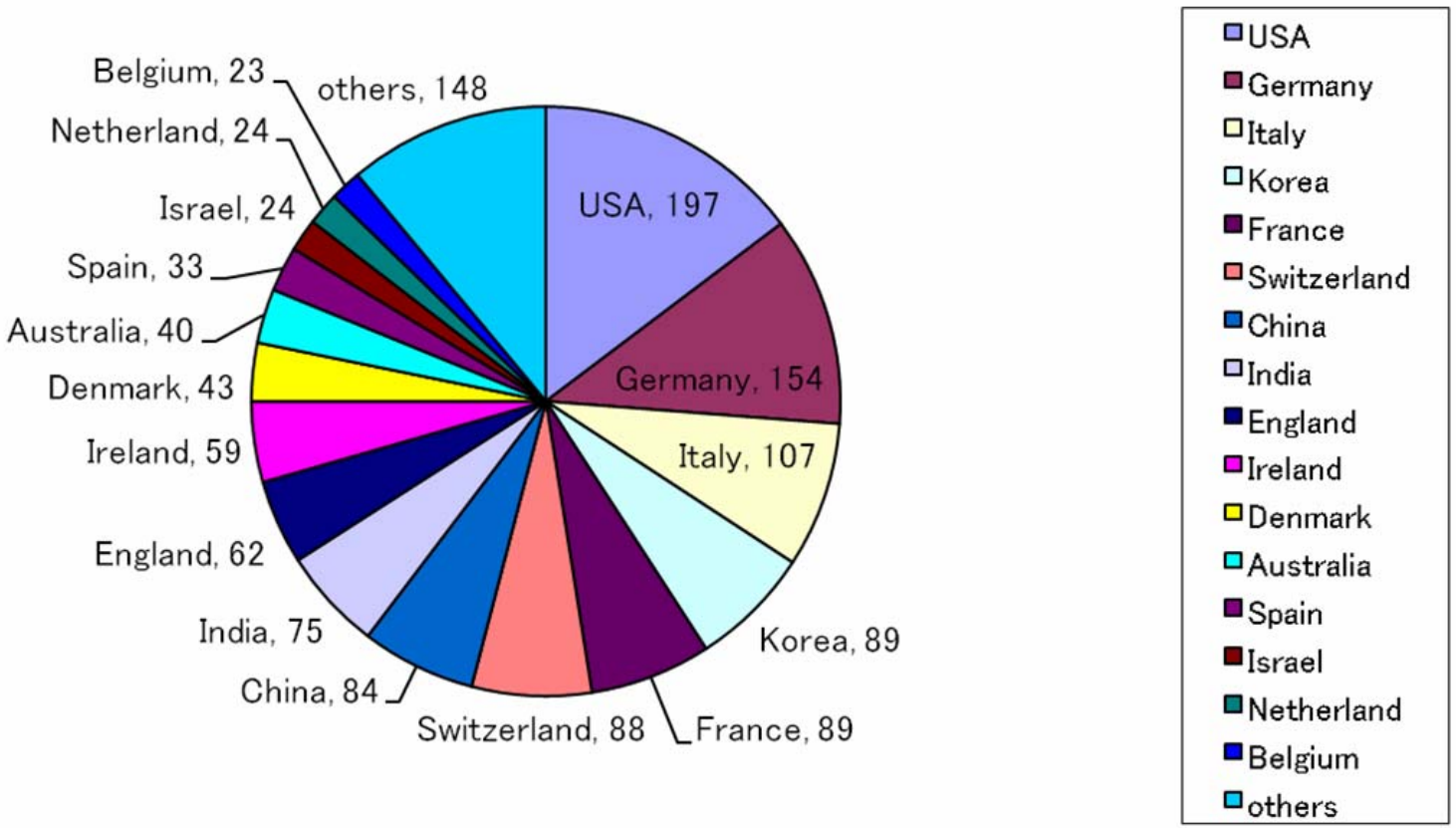
Requests for document inspection (cont.)

9. Report of process validation (report of full scale production batches)
10. Report of cleaning validation
11. Manufacturing history (batch number, date of manufacture and batch size) or intended annual manufacturing schedule
12. Copy of deviation control procedure and summary of actual deviation events (for past two years)

Requests for document inspection (cont.)

13. Copy of change control procedure and summary of actual changes occurred in the past two years
14. Copy of release procedure
15. Document (s) describing the status for compliance to the Standards for Biologically derived raw materials
16. (Site Master File)

Actual number of GMP inspections for foreign manufacturer (Apr.2005-Jan.2008)



Total number of applications：2144, Number of domestic applications：657

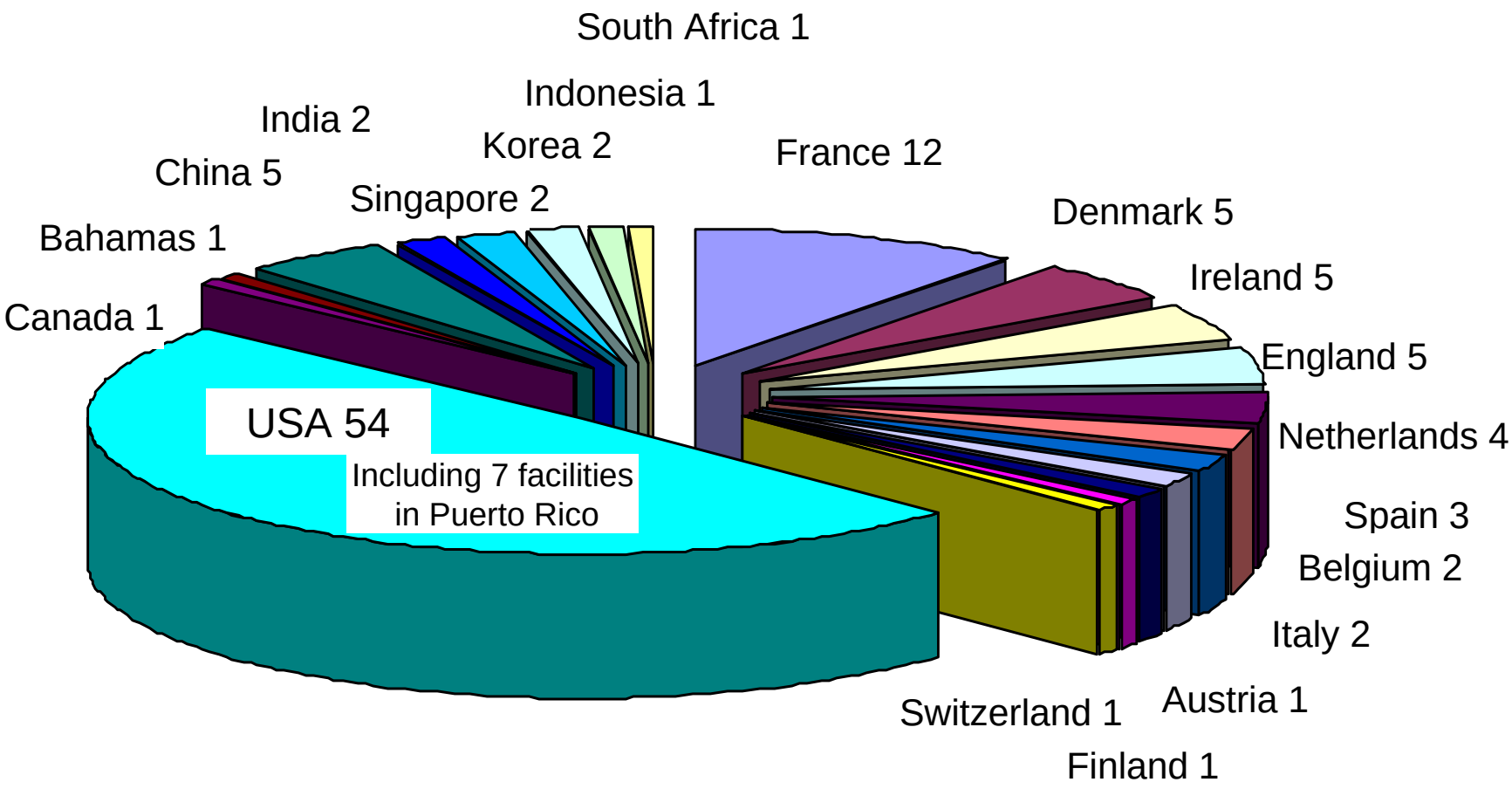
On site inspections for foreign facility

○Areas

April.2005-March.2008

Area	EU	North America	Central and South America	Asia	Other	Total
Drugs	41	55	1	12	1	110
Medical Devices	7	23	0	0	0	30
Total	48 (34%)	78 (56%)	1 (1%)	12 (9%)	1 (1%)	140 (100%)

On site GMP inspections for foreign facilities (Apr.2005 – Mar.2008)



37 Persons : Number of GMP inspectors in PMDA (1. Apr. 2008)

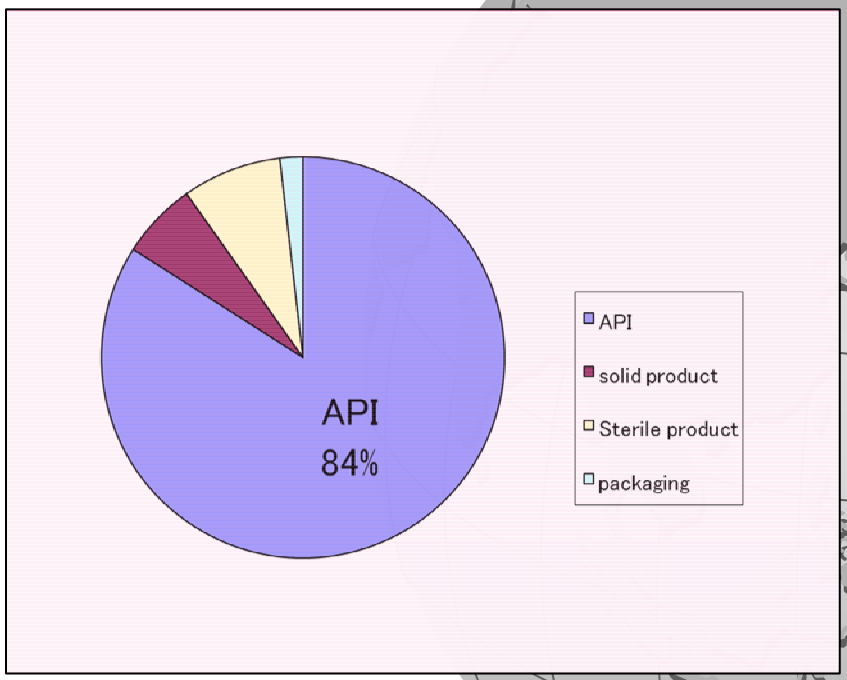
On site inspections for foreign facility

○Category

April.2005-March.2008

Category	EU	North America	Central and South America	Asia	Other	Total
Sterile drugs, Biologics	23	30	0	2	0	55
Solid products	1	8	0	2	0	11
API (chemicals)	17	7	1	8	1	34
Packaging site, testing labs	0	10	0	0	0	10
Total	41	55	1	12	1	110

Summary of GMP inspections for generic product (Apr.2006-Mar.2008)

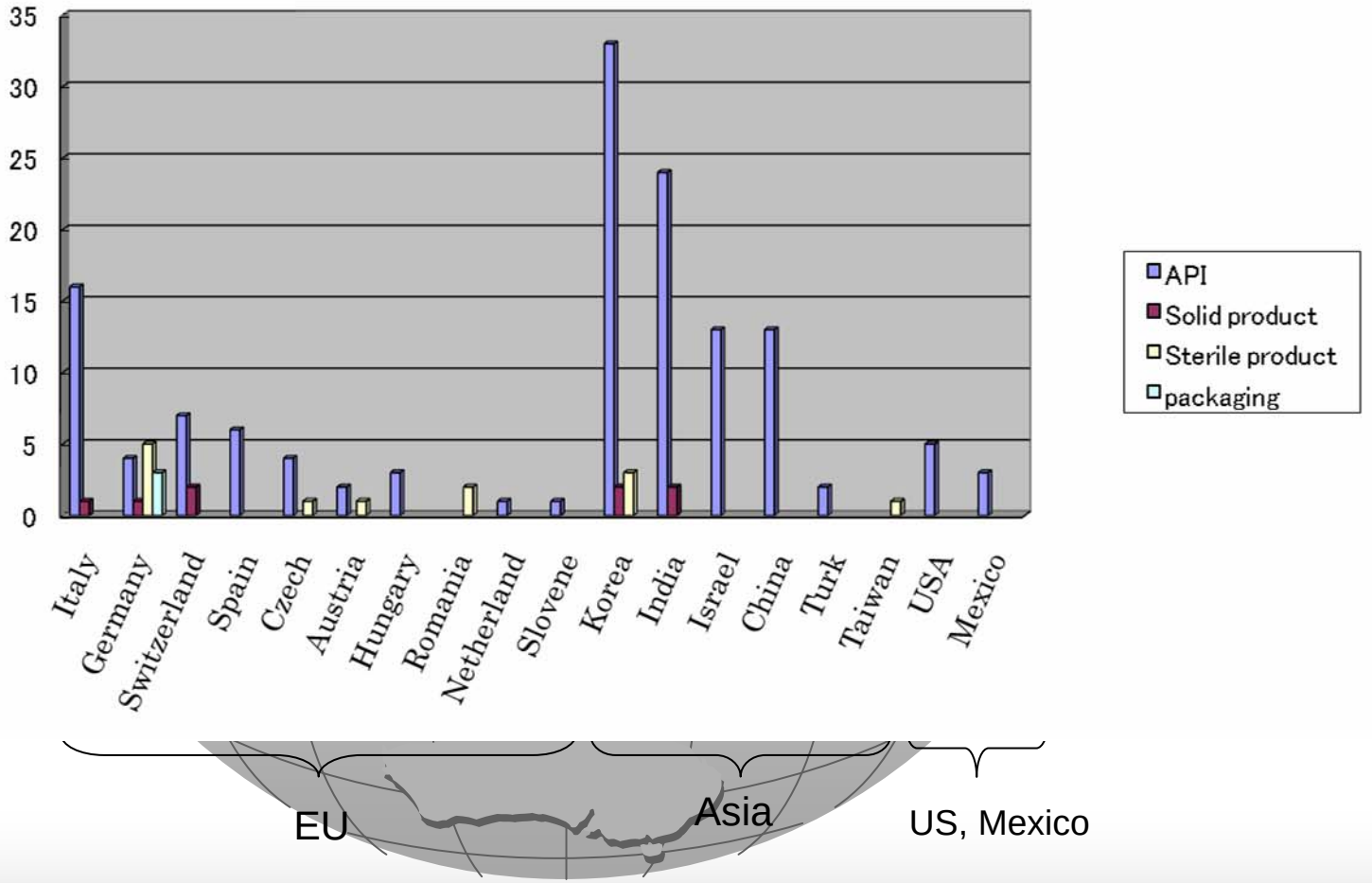


Category	Number	Area	Number
API	137	EU	46
		Asia	83
		USA, Mexico	8
Solid Product	10	EU	3
		Asia	7
Sterile Product	13	EU	10
		Asia	3
Packaging	3	EU	3

Total number of approved generic product:163

About 84% (137) : API

Summary of GMP inspections for generic product (Apr.2006-Mar.2008)



API: Korea, India, Italy, China・・・・

Problems experienced in foreign on site inspection

- **Insufficient concern of Japanese marketing approval holder in control of manufacturer**
- **Nonconformity to the Japanese Standards for Biological ingredients**

framework of the Japanese international cooperation

Present framework of the Japanese international cooperation of Japan

- Mutual Recognition Agreement with EC
- Memorandum of Understanding
- Drugs for export (Article 80 of PAL)

Mutual Recognition Agreement with EC

- **Come into effect on 29.May.2004**
- **Mutual Acceptance of GMP inspection for manufacturing site and certificate of analysis for each batches of products**
- **Country: Belgium, Denmark, Germany, Greece, Spain, France, Ireland, Italy, Luxembourg, Netherlands, Austria, Portugal, Finland, Sweden, United Kingdom**

MoU (Memorandum of Understanding)

- **Cooperation for issuance of inspection reports, etc**
- **Pharmaceuticals: Germany, Sweden, Switzerland, Australia**

*** Under review of the current status by MHLW**

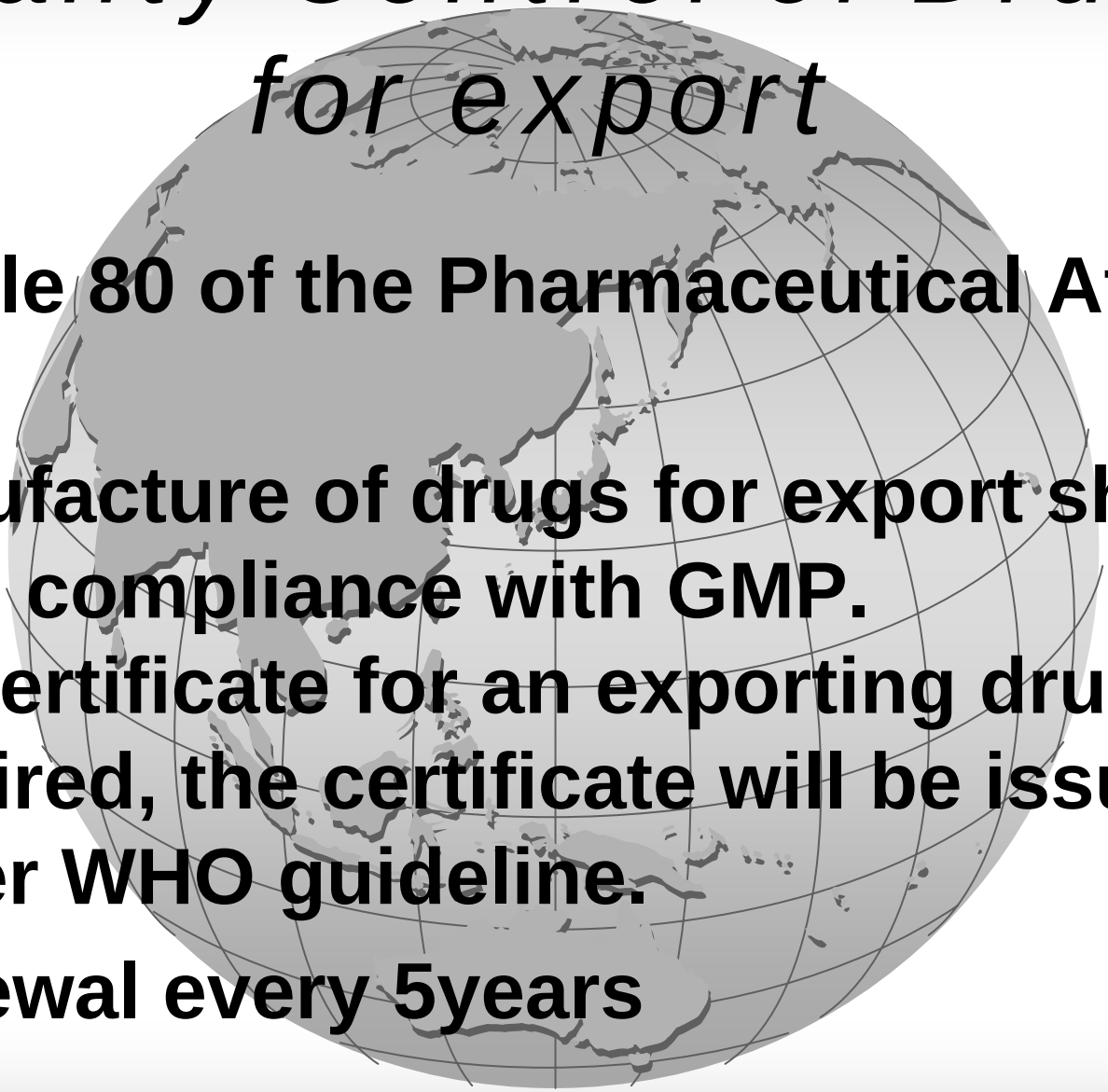
GMP Inspection for Foreign Sites

- **MRA*: Document inspection only for pharmaceuticals except sterile products and biologics**
- **MOU*: Document inspection only for Pharmaceuticals**

MRA* Japan-EU Mutual Recognition Agreement (API: out of scope)

MOU* Memorandum of Understanding between Japan and Australia, Germany, Sweden, Switzerland

Quality Control of Drugs for export



- **Article 80 of the Pharmaceutical Affairs Law**
- **Manufacture of drugs for export shall be in compliance with GMP.**
  If a certificate for an exporting drug is required, the certificate will be issued under WHO guideline.
- **Renewal every 5years**

Future efforts

Points to consider

(1) Developing a scheme on cooperation among stakeholders

(2) Understanding of regulations of each country

(3) Resource (Increase of number of inspectors, etc)

(4) Training of Inspectors

(5) Mutual benefit

(6) Collaboration with MHLW on expansion of scope of MRA with EU

(7) ICH, PIC/S, other activities


Thank you for your attention.
pmda
Pharmaceuticals and Medical Devices Agency
http://www.pmda.go.jp/