GMP and QMS Regulation in Japan

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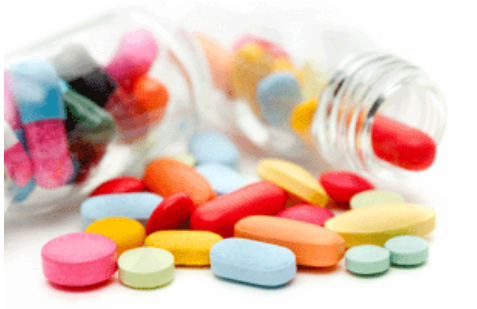
1st Brazil-Japan Seminar

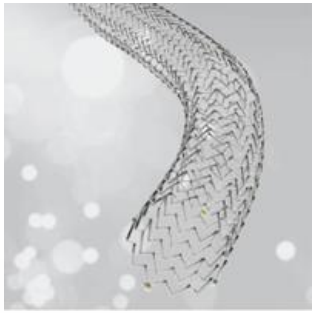
GMP/QMS

■GMP：Good Manufacture Practice



Standards for Manufacturing Control and Quality Control for Drugs

■QMS：Quality Management Sysytem



Standards for Manufacturing Control and Quality Control for Medical Devices and In-vitro Diagnostic Reagents

GMP/QMS

- When manufacturing a drug or a medical device, all products should be of the same quality as that of the product which was approved.

- To ensure this, the manufacturing site should have appropriate facilities, and its quality management system should be maintained and controlled properly.

GMP/QMS

- Manufacturers need to be in compliance with the Japanese GMP or QMS.
- Manufacturers will be inspected by PMDA or prefectural governments for the GMP/QMS either on-site or by document review (document inspection) .
- The first inspection will be conducted before approval.

Quality Control Regulation on Drugs

GMP

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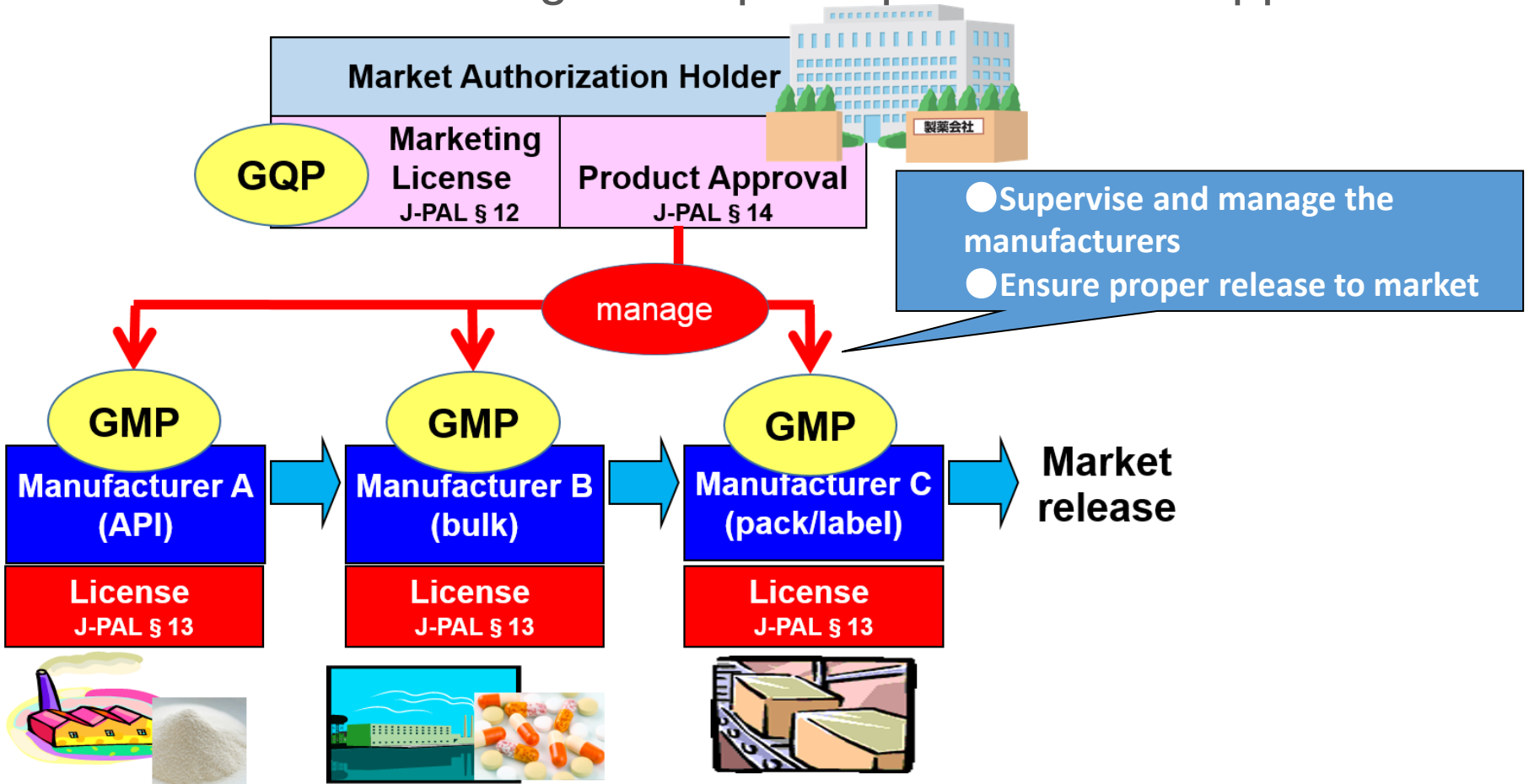
GQP and GMP for Drugs

- MAH shall have the marketing license and GQP(Good Quality Practice) is prerequisite for the license. And also MAH shall have product approval and GMP compliance at each manufacturing site is prerequisite for the approval.



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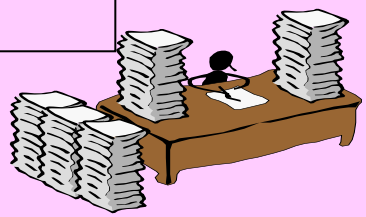
Review & Inspection

Application of New Drug



Review

New Drug

Application form

Submission

Pilot scale Data

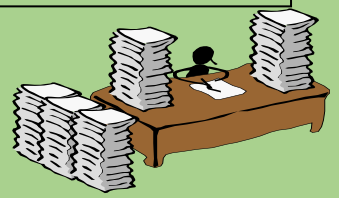
Re-submission

Production scale Data

Pre-Approval Inspection

Approval

Application of Partial Change (PC) of Approval



Review

Application of PC

Pre-Approval Inspection

Production Based on Approval

5-yearly Inspection

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GMP Inspection Authorities

MHLW

（manufacturing license, marketing license, marketing authorization, administrative order, pharmacovigilance, license withdrawal, seizure, penalty, etc.）

management and policy development function. In general, only inspection that MHLW conducts with its 8 regional branches is a for-cause inspection.

PMDA is partially vested authority from MHLW (assessment , GMP inspection, information gathering)

Prefectures are vested part of MHLW's authority to have local autonomy.

PMDA

Inspectorate

Prefectures

47 Inspectorates

GMP Inspection Authorities

- GMP inspections for pharmaceutical products are conducted by PMDA and prefectural governments as below.

	Domestic	Overseas
New drugs, Biological products, Radio pharmaceuticals	**PMDA**	**PMDA**
Other drugs	Prefectural governments	**PMDA**

Types of GMP/QMS Inspection

- Compliance inspection

  1 Pre-approval inspection
  - Based on application
  - One of the requirements for marketing approval
  - Conducted per a product

  2 Post-approval inspection
  - Based on application
  - Conducted every five years after marketing approval
  - Basically, Conducted per facility

- For-cause inspection

The number of manufacturing sites that the PMDA inspects

As of April 2014

Foreign manufacturing sites

Approximately 3,500

- Accredited sites: 3165
  Asia (excluding Japan) and the Middle East: 1203 (drugs: 1025, quasi drugs: 178)
  Europe: 1257 (drugs: 1179, quasi drugs: 78)
  North America, Central and South America, Africa, Oceania: 705 (drugs: 639, quasi drugs: 66)
- Others: Approximately 300

  (API intermediates, APIs made from food products or other industrial products, etc)

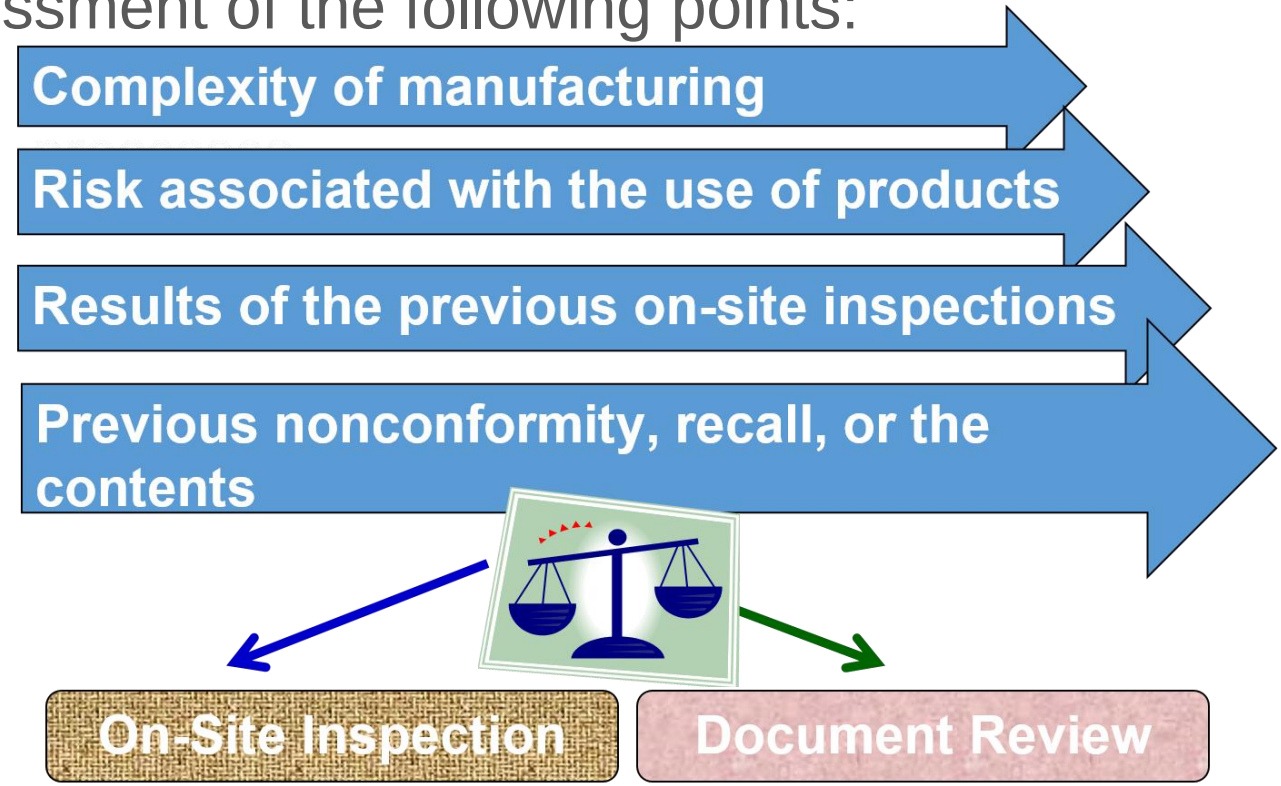
Domestic manufacturing sites

Approximately 440

- Licensed by the Minister: 87
  Biological products: 67
  Radiopharmaceuticals: 20
- Licensed by the prefectural governor; Approximately 350 new drugs

On-site Inspection and Document Review

- On-site inspection is conducted based on the risk assessment of the following points:

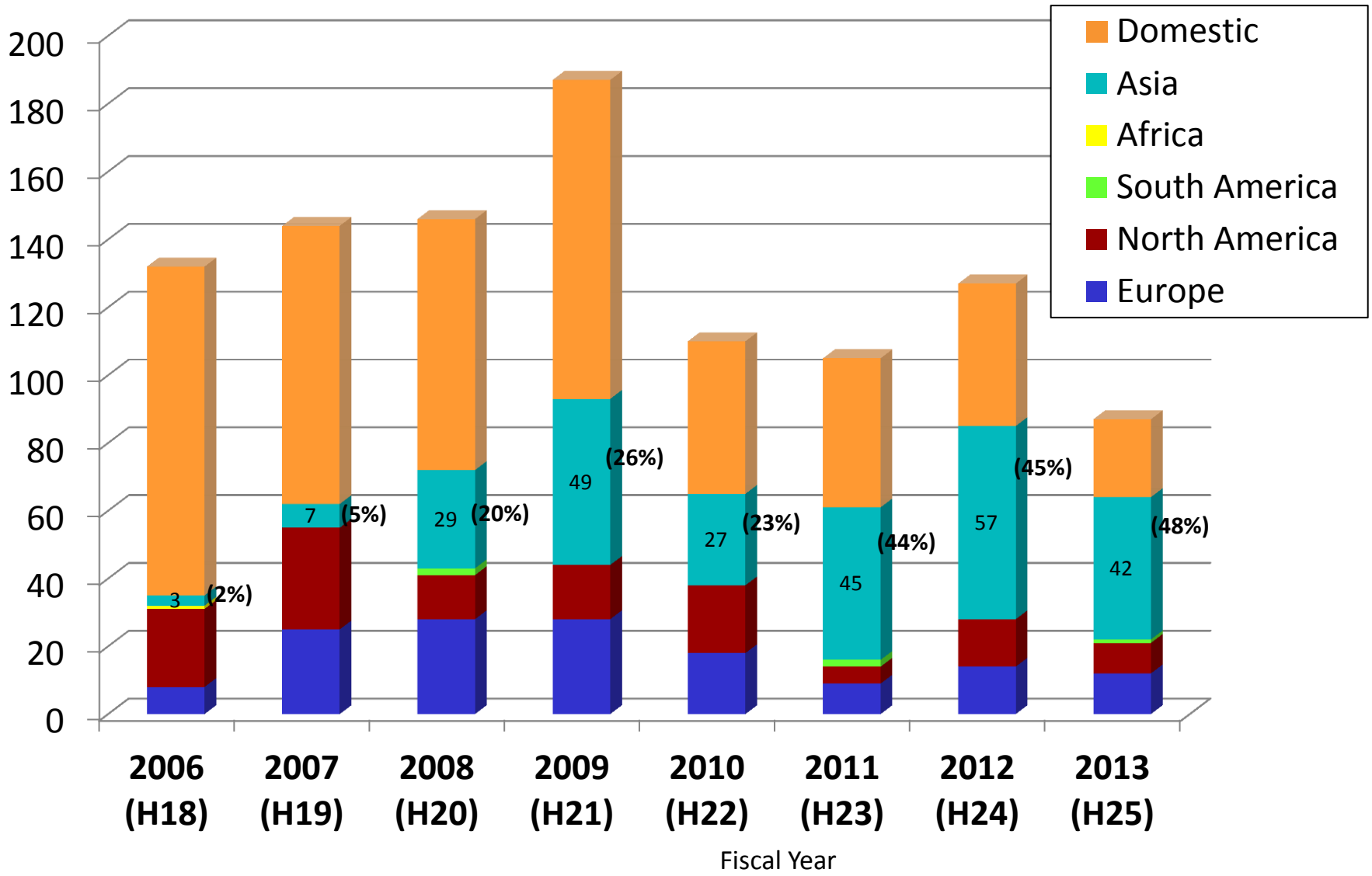


Manufacturing sites located in the countries with MRA or MOU are generally subjects for document reviews.

MRA: Mutual Recognition Agreement
MOU: Memorandum of Understanding

Number of GMP On-site Inspections

(April 2006 –March 2014)



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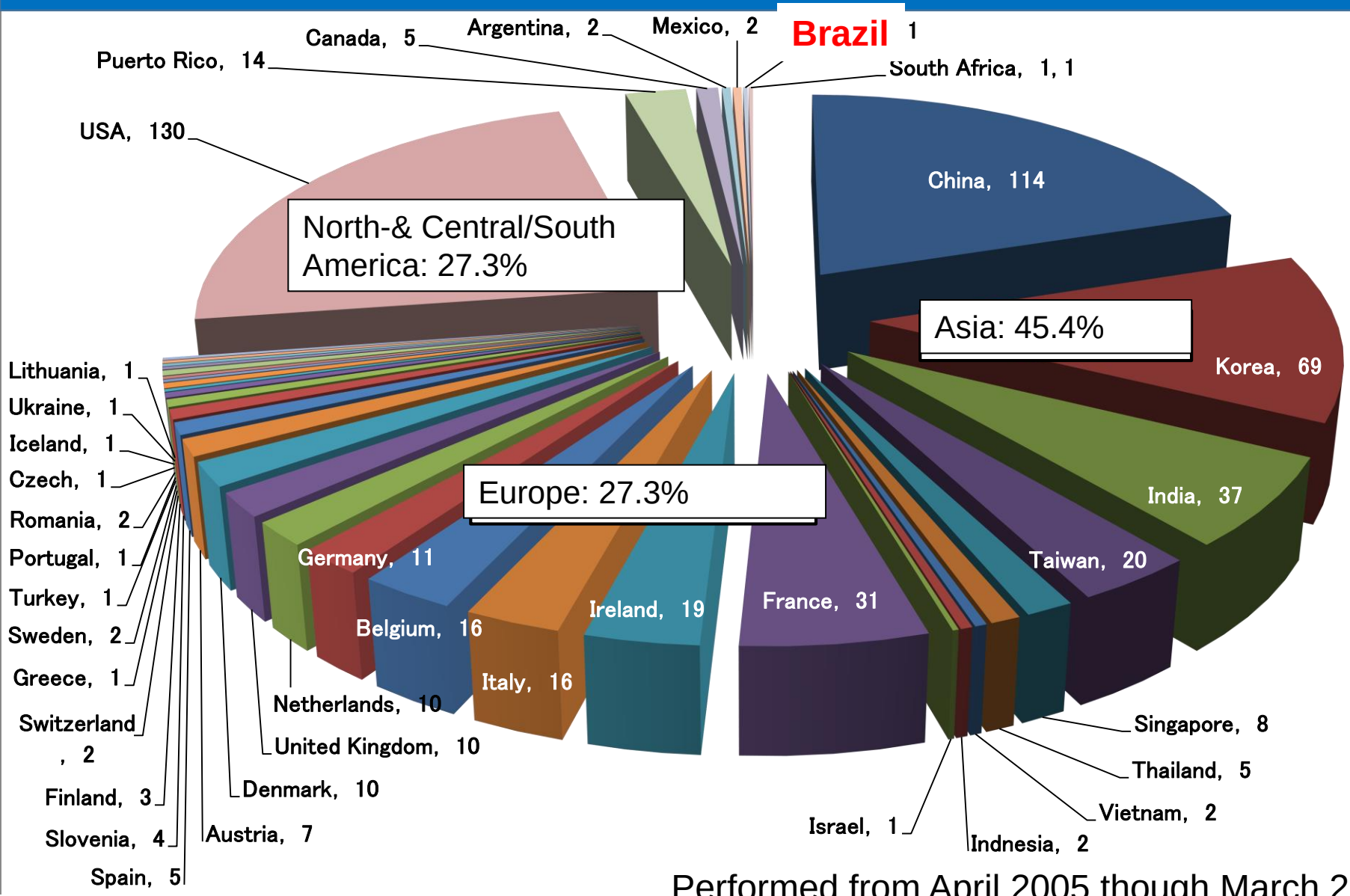
Number of GMP Overseas Inspections



Performed from April 2005 though March 2014
(No. of Manufacturing Sites: 568 in 38 countries)

History of International Cooperation of GMP

- MOUs on GMP certificates and mutual recognition of QC data
  - 1986 September with Western German authority
  - 1987 July with Swedish authority
  - 1988 June with Swiss authority
- EOLs on cooperation for exchanging GMP inspection reports
  - 1993 April with Australian authority (TGA)
  - 2000 December with U.S. authority (FDA)
- May 2004 Japan-EC (EU) MRA, GMP Sectoral Annex was enacted after both parties confirmed equivalence of their GMP implementation. （15 countries, solid dosage form)
- July 2014 GMP authorities of Japan, i.e. MHLW, PMDA and 47 prefectural governments became the official member of PIC/S.

MOU：Memorandum of Understanding
EOL: Exchange of Letter

Link with EudraGMDP

- Since 1 Oct. 2013, MHLW and PMDA have started entering GMP-compliance information on Japanese manufacturers, upon their requests, into EMA's "EudraGMDP" DB.

- According to EMA's website, this is **the first time** that information from non-EEA regulatory authorities is added to the DB.

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PIC/S

PIC/S: Pharmaceutical Inspection convention and
Pharmaceutical Inspection Co-operation scheme

- Cooperative framework between GMP inspectorates aimed to achieve harmonized GMP standards within the pharmaceutical area and the international development, enforcement, and conservation of the quality system.
- PIC/S's objectives:
  "Development and maintenance of harmonized GMP guidelines and Quality system of authorities"
- Membership: Many EU nations, including US FDA.
  46 organizations(43 countries)
- PIC/S is emerging to become the world standard in the GMP domain.

Membership of PIC/S

- Japan became the 45th official member on July 1st, 2014.
  - Japan（MHLW, PMDA, 47 prefectures）GMP Inspectors applied for PIC/S membership on March 2012.
  - Decided to become an official membership on July 1st 2014 at the 38th PIC/S committee meeting on May 15-16, 2014（Rome）.

With PIC/S Chair Dr. Joey Gouws

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Quality Control Regulation on Medical Devices

QMS

After the revision of the Law, November 2014

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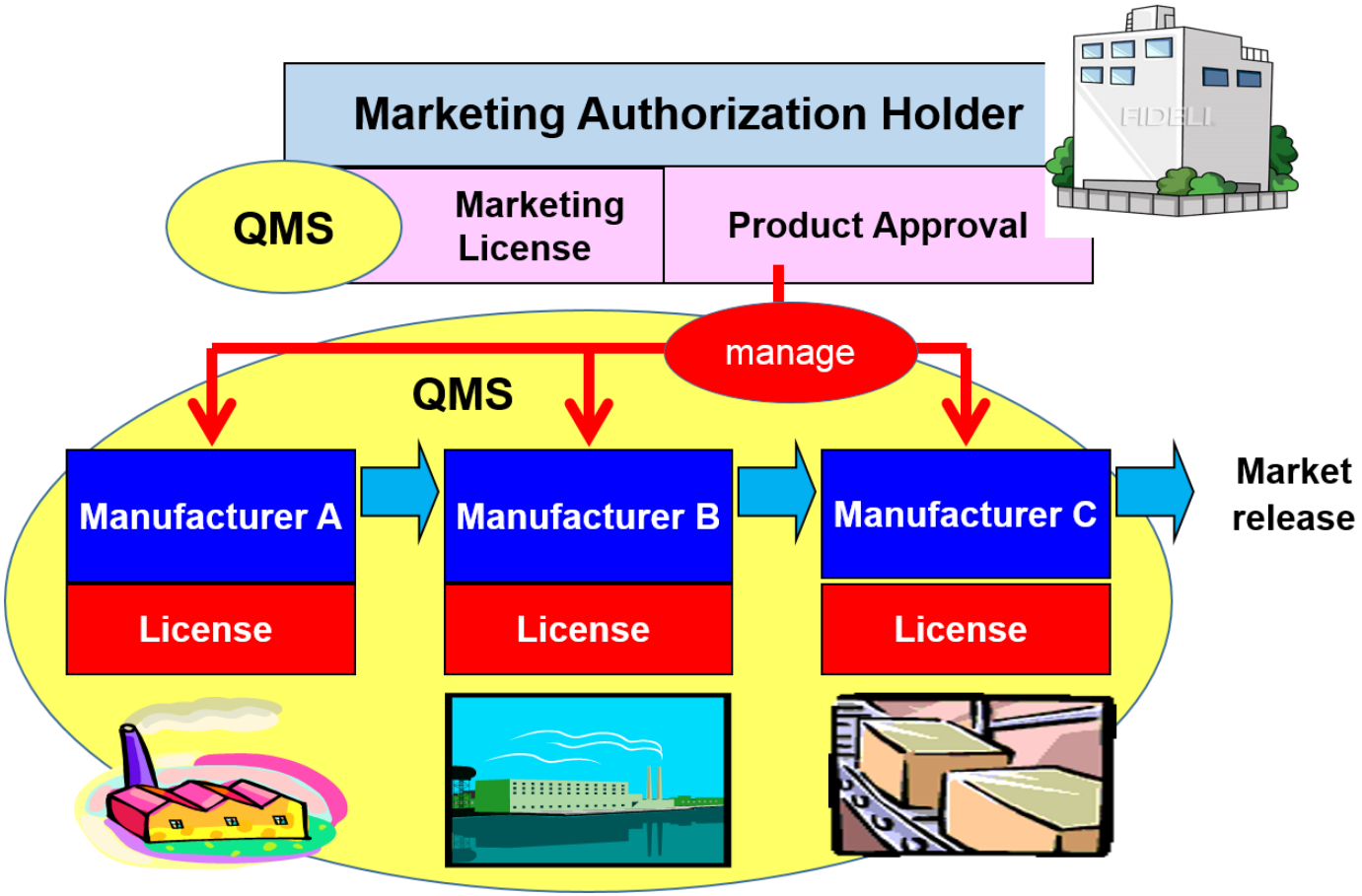
QMS for Medical Devices

- MAH shall have the marketing license and some parts of QMS is prerequisite for the license. And also MAH shall have product approval and the other parts of QMS for whole manufacturing is prerequisite for the approval.



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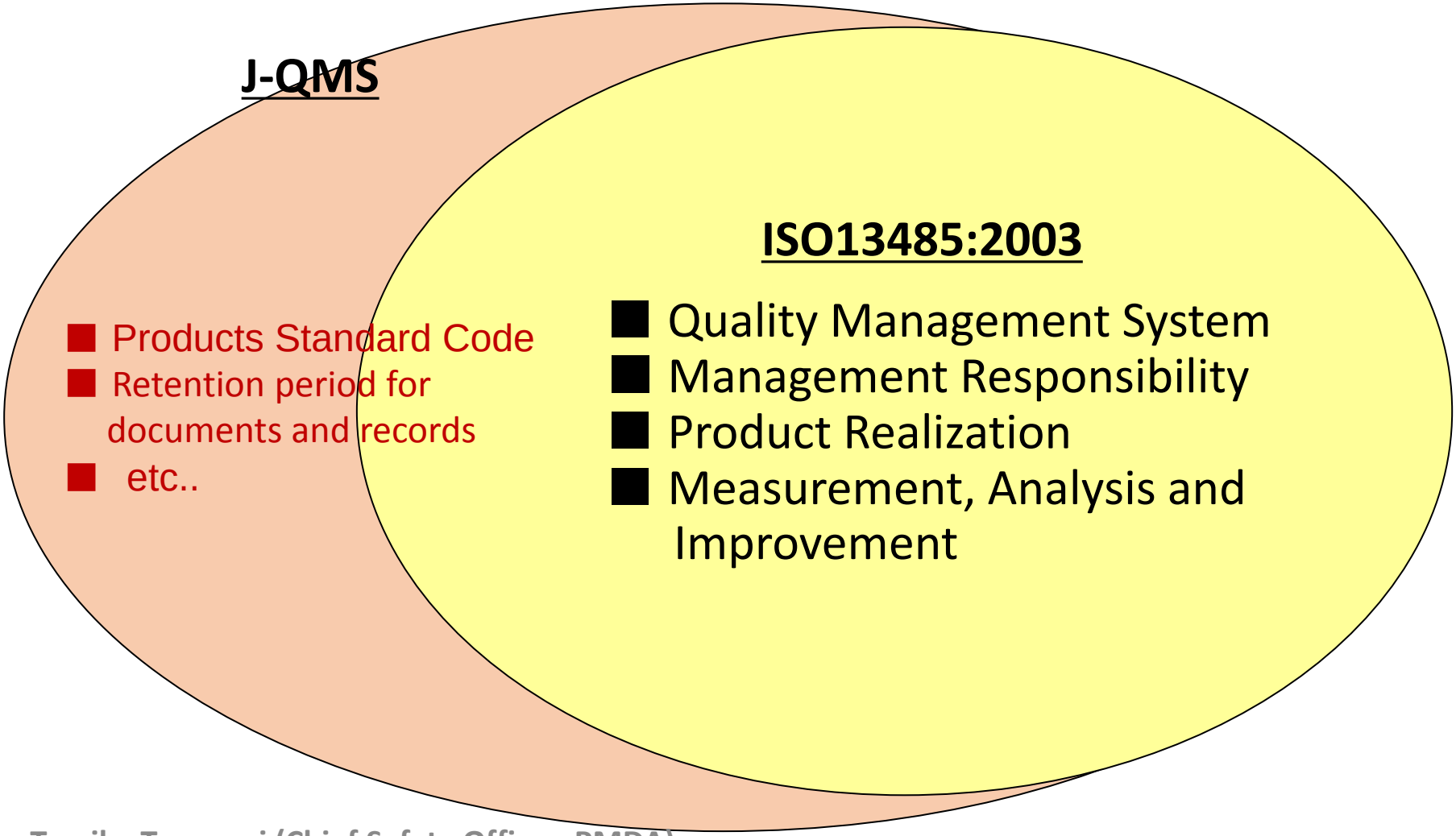
J-QMS and ISO13485:2003

Main parts of J-QMS is substantially harmonized with ISO13485.
There are some additional requirements by J-QMS.



QMS Inspection Authorities

		Domestic	Foreign
IVDs	・New IVDs ・Radioactive IVDs	PMDA	PMDA
	Products without CS*	PMDA	PMDA
	Products with CS*	Registered certification body	Registered certification body
Medical Devices	・New medical devices ・Cell / Tissue-based medical devices ・Class Ⅳ products	PMDA	PMDA
	Class Ⅲ and Class Ⅱ products (without CS*)	PMDA	PMDA
	Class Ⅱ products (with CS*)	Registered certification body	Registered certification body

*CS : Certification Standards

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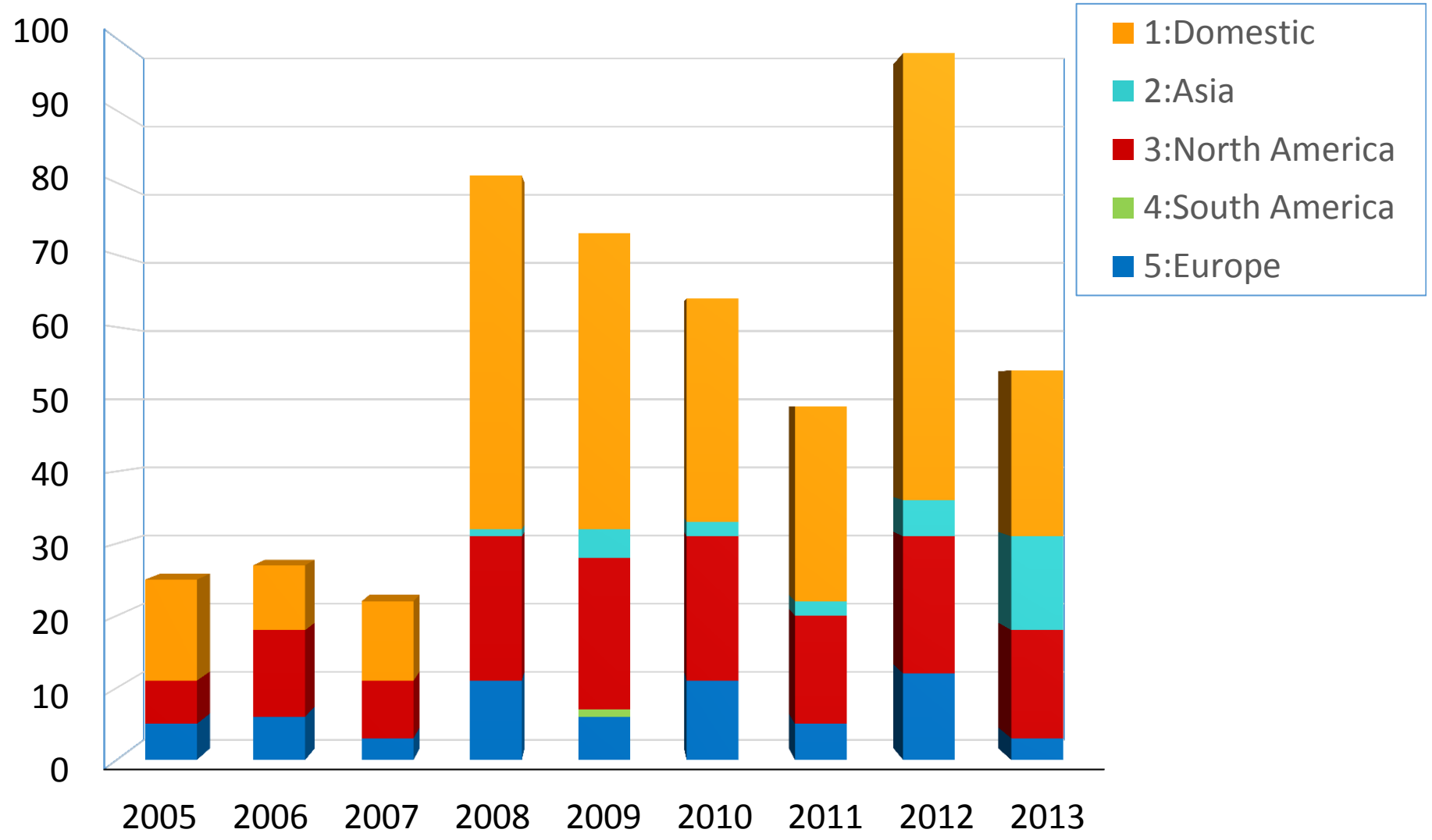
Number of QMS On-site Inspections



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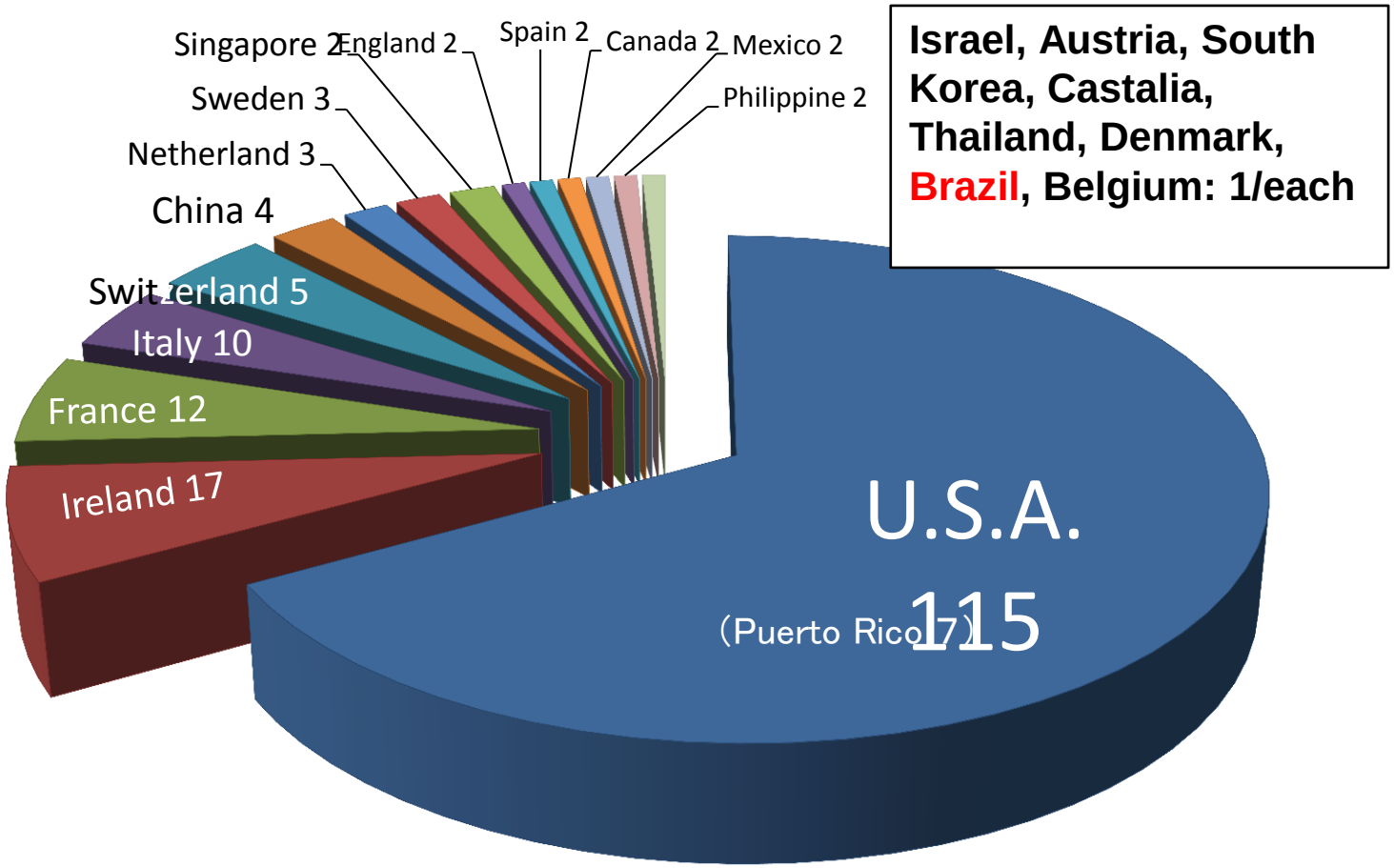
Number of QMS Overseas Inspections

Total number of foreign on-site inspection
【189 inspections/22 countries】



Israel, Austria, South Korea, Castalia, Thailand, Denmark, Brazil, Belgium: 1/each

From 2005 - 2012

International Cooperation

- IMDRF (International Medical Device Regulators Forum) is developing a standard set of requirements for auditing organizations performing regulatory audits of medical device manufacturers' quality management systems.
- US FDA, Brazil, Canada and Australia have initiated a new pilot program of MDSAP (Medical Device Single Audit Program).
- Japan is an official observer and an active participant in the Pilot Program's Regulatory Authority Council and subject matter expert groups since 2013.