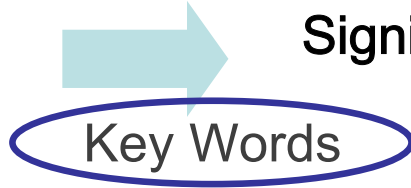


Presentation on the new Japanese Pharmaceutical Affairs Law Overview

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January, 2005

Overview of Important Changes in the Revised PAL

Significant Changes in Regulations



Key Words

International Harmonization
and Securing Safety and Safety Measures

1. Change in approval and license systems

Marketing Authorization Holder System introduced

2. New classification according to risk

- (1) Class IV/III
- (2) Class II
- (3) Class I

Third part certification system introduced for the specified Class II medical devices.

3. Enhancement of post-market safety measures

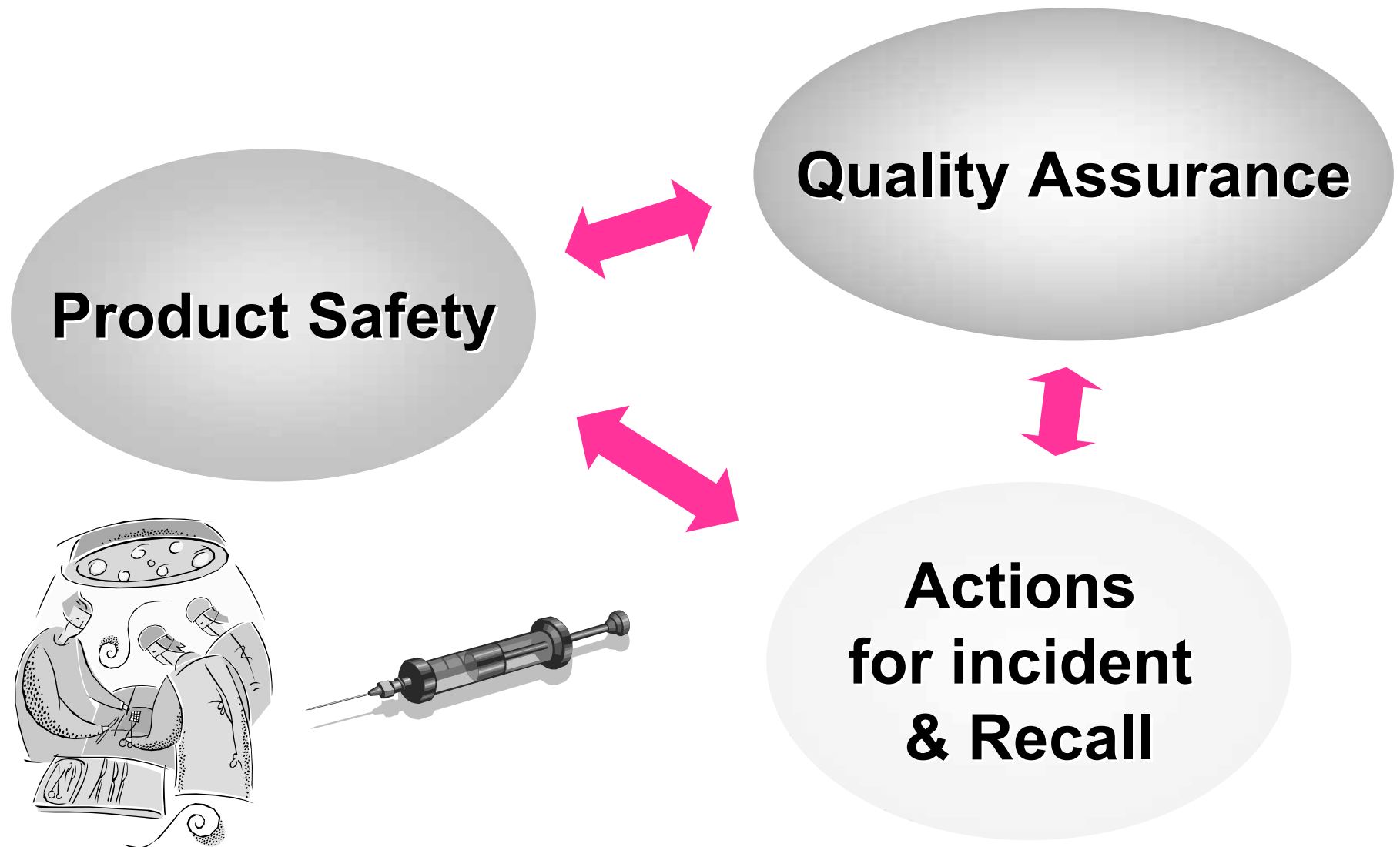
Companies shall have ultimate responsibilities for securing safety and obtaining quality of medical devices in the market place.

What is Pharmaceutical Affairs Law ?

- Established in August 1960
- The latest version was published in June 2003, and will be enforced on April 1, 2005

- Scope
 - Pharmaceuticals
(including *in vitro* diagnostic reagents)
 - Sanitary & toiletry products
 - Cosmetics
 - Medical devices

Regulatory Requirements for Medical Devices Regulations

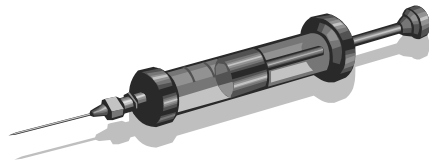


Regulatory Requirements for Medical Devices Regulations

Internationally agreed platform
through GHTF activities

**Essential Requirements
(+ Risk Analysis)**

**Adopted in Japanese
new PAL**



Use of ISO 13485

**Adopted in Japanese
new PAL**

Clarified reporting rules

GHTF SG 2

Overview of Medical Devices Regulations

	Organization	Product Safety	QMS	Reporting
USA	FDA	510 k PMA	QSR	MDR
Japan	MHLW + PMDA & Local Gov. + 3 rd Party	Pre-market Device Approval	GMP (ISO13485: 2003)	Adverse events reporting
EU	Competent authorities of member states Notified Body	MDD CE Marking	MDD EN ISO13485	MDD Vigilance System
Canada	Health Canada Registrar	CMDR Device License	CMDR ISO13485	CMDR

Japanese Pharmaceutical Affairs Law

Organizations involved

- MHLW (Ministry of Health, Labor and Welfare)
- PMDA (Pharmaceuticals and Medical Devices Agencies)
- Local Government
- 3rd Party Cert. Bodies

Japanese Pharmaceutical Affairs Law

Basic Requirements of PAL

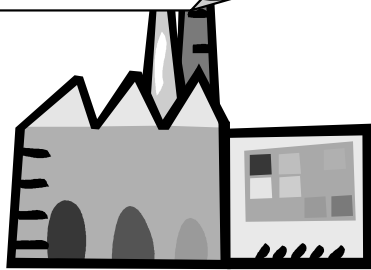
- “KYOKA” = Business Licenses
 - License for MAH (Market Authorization Holders)
 - License for Manufacturing Facilities
- “SHONIN / NINSHO” =
Pre-market Device Approval / Certification

Classification = Class I, II, III, IV

- Class I, Notification
- Class II, Certification by 3rd Party Cert. Body
- Class III & IV, Approval by the Government

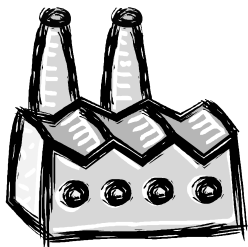
Requirements for Business Licenses

License

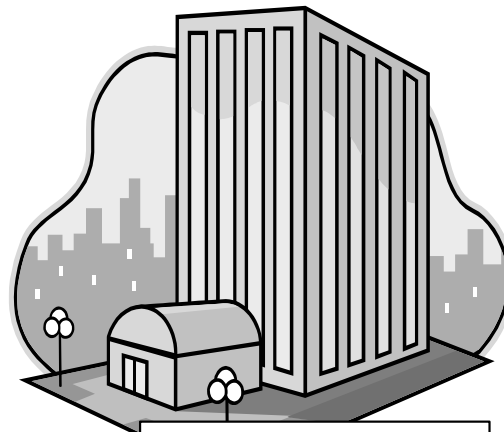


**Manufacturing
Facilities in
Japan**

Registration

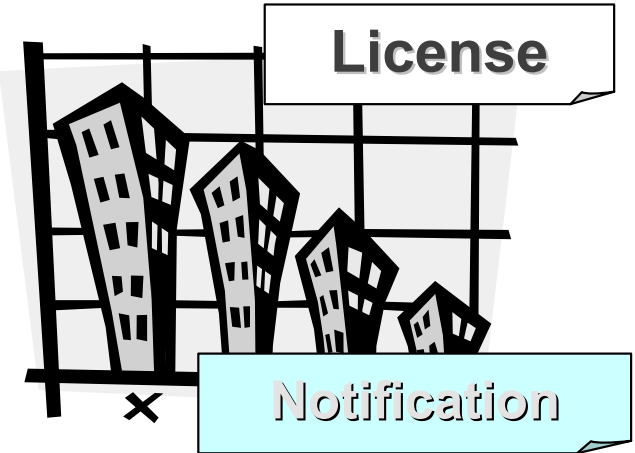


**Foreign
Manufacturing
Facilities**



License

**Marketing
Authorization
Holder
(MAH)**



Sales Branches

License



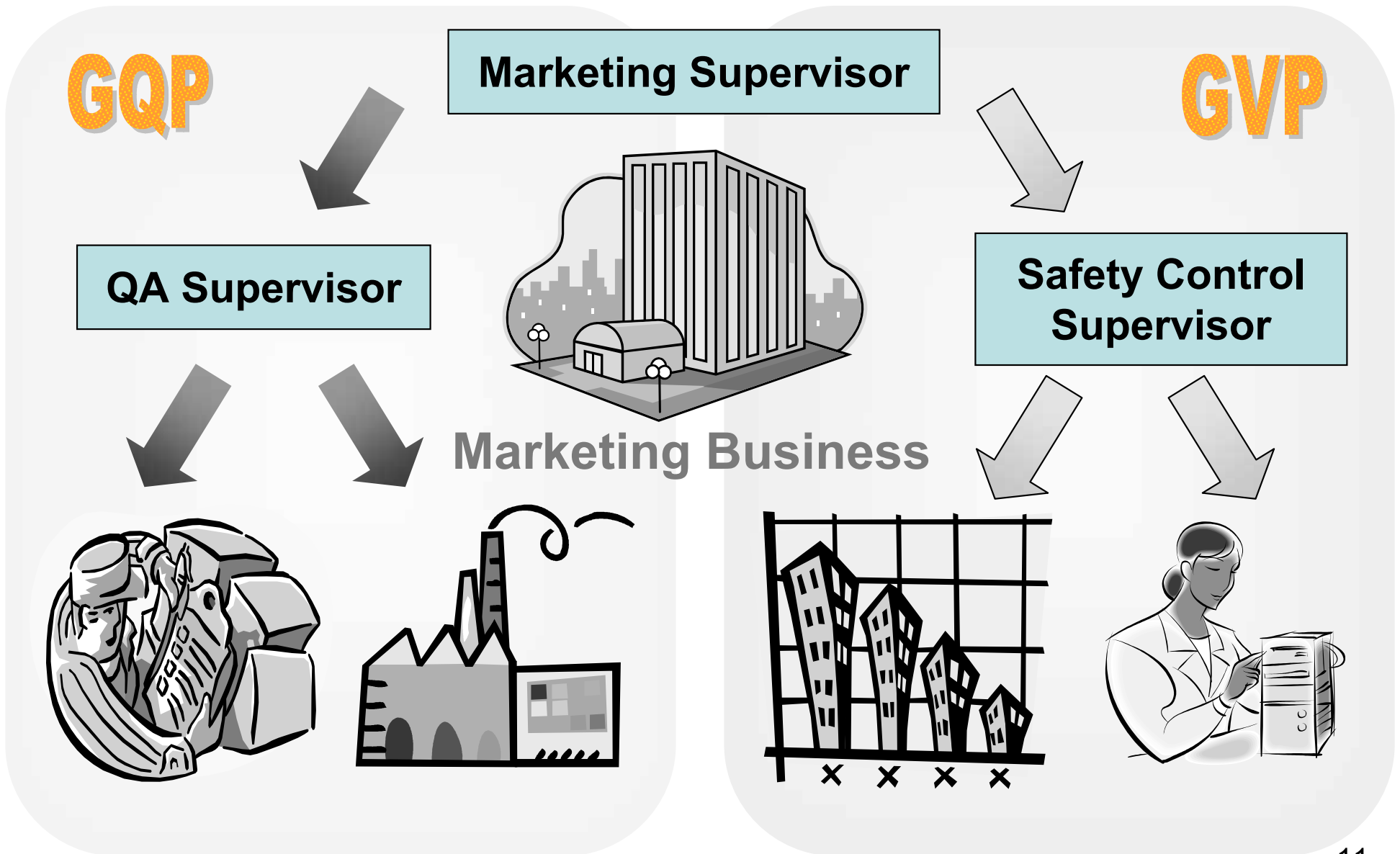
Repair Centers

Requirements for MAH Business License

- MAH must be in Japan
- GQP : Good Quality Control Practice
- GVP : Good Vigilance Practice
- 3 Supervisors must be assigned
 - ✓ Marketing Supervisor
 - ✓ QA Supervisor
 - ✓ Safety Control Supervisor



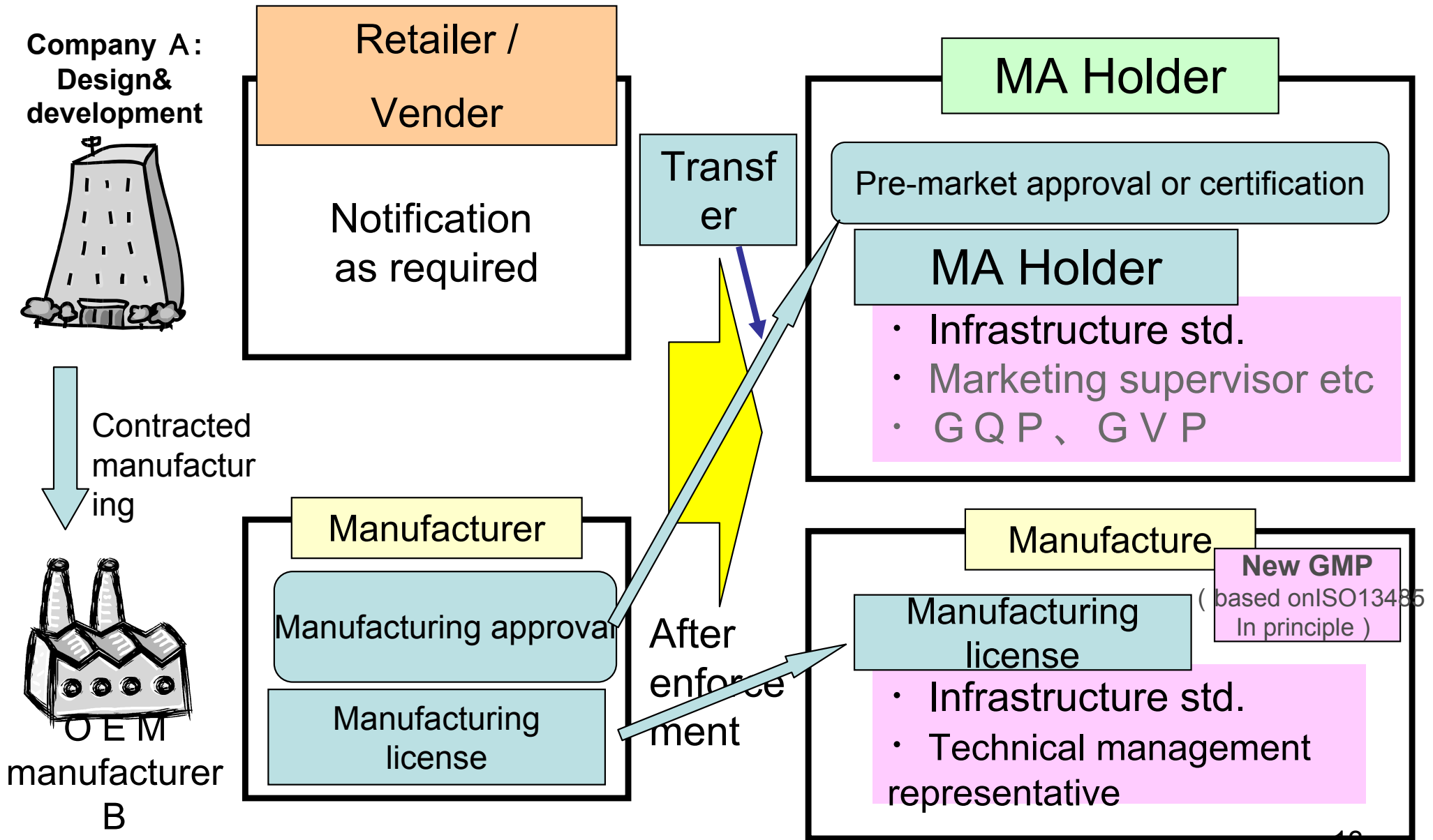
GQP and GVP / role of supervisors



Current Manufacturer

- After the enforcement of the Revised PAL in April,2005, the current manufacturer must meet the following regulatory requirements.
- (1)As Marketing Authorization Holder (MAH)
- Marketing Supervisor+QA Supervisor+Safety Control Supervisor
- Conforming to GQP and GVP
- (2) As Manufacturer
- Continue to apply the current GMP for the current approved products until the expiration date of the current license.
- Pre-market approval of a new product shall require the conformity to the new GMP.

Current Manufacturer shall be changed to Manufacturer and/or MAH



How the requirements of ISO 13485: 2003 be used in Japanese under new Pharmaceutical Affairs Law

1. ISO or Regulation ?

Japanese new PAL will be enforced in April 2005, adopting ISO 13485: 2003. It does not mean that manufacturers must get ISO 13485:2003 cert. by April 2005. Not directly ISO 13485, but the QMS regulation (called GMP) is used for auditing. The requirements are equivalent to ISO 13485:2003 but not completely identical.

2. When an audit is conducted ?

The audit with the new QMS regulations will be triggered by the submission of a pre-market device application in or after April 2005. Any medical device manufacturer will NOT face the new style audit before the first submission of pre-market application.

3. What happens if the audit results are not positive ?

The manufacturer can not get the approval of that newly submitted application. The approval status of the existing medical devices, as well as the license / registration status, will not be influenced (though there would be exceptional cases depending on audit results).

Japanese Pharmaceutical Affairs Law

Case study 1

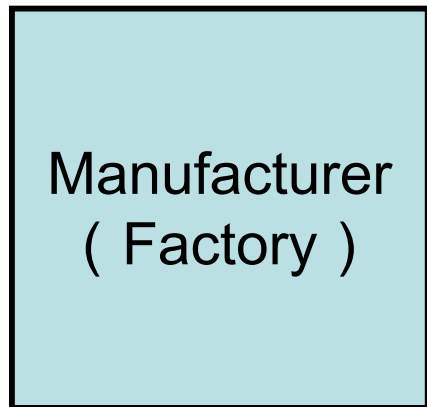
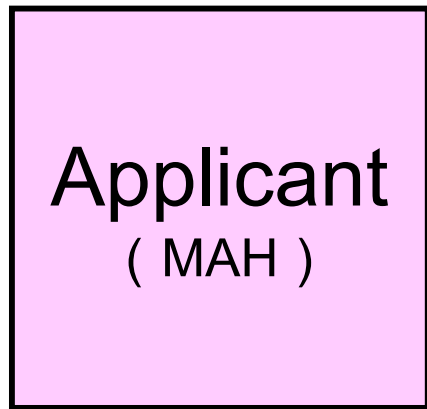
A Medical Device Manufacturer in Japan with 2 facilities
(HQ & a Manufacturing facility) for Class II devices

-> What the company should do ?

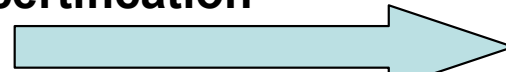
- ❑ Obtain “KYOKA” (Business Licenses)
- ❑ HQ needs license for “Marketing Authorization Holder”
- ❑ The manufacturing facility needs license for “Manufacturing facility”
- ❑ Obtain “NINSHO” (Device certification)
- ❑ HQ submits Pre-market application to a 3rd Party Cert. Body
- ❑ Triggered by the submission of Pre-market application, a QMS audit will be conducted by 3rd Party Cert. Body at the manufacturing facility

Third party certification assessment system

Class II specified by MHLW



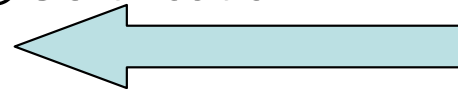
① Appn for product certification



② Appn for GMP inspection



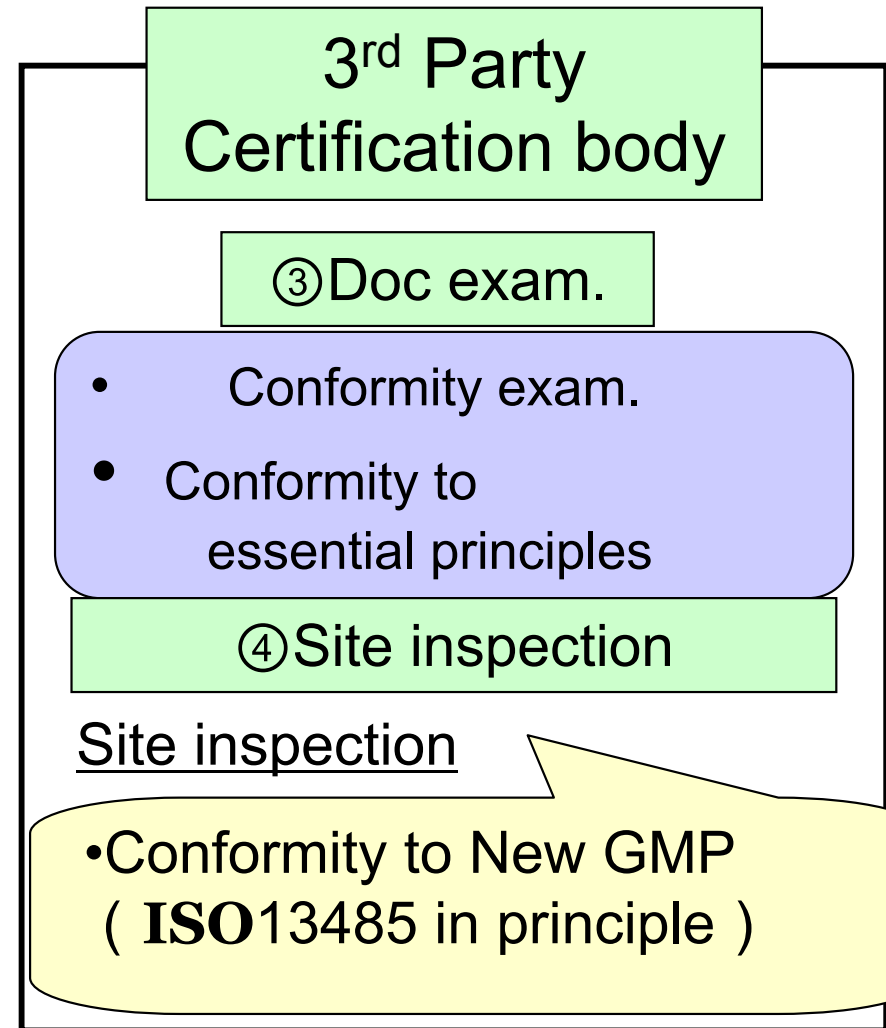
⑤ Certification



④ Site inspection

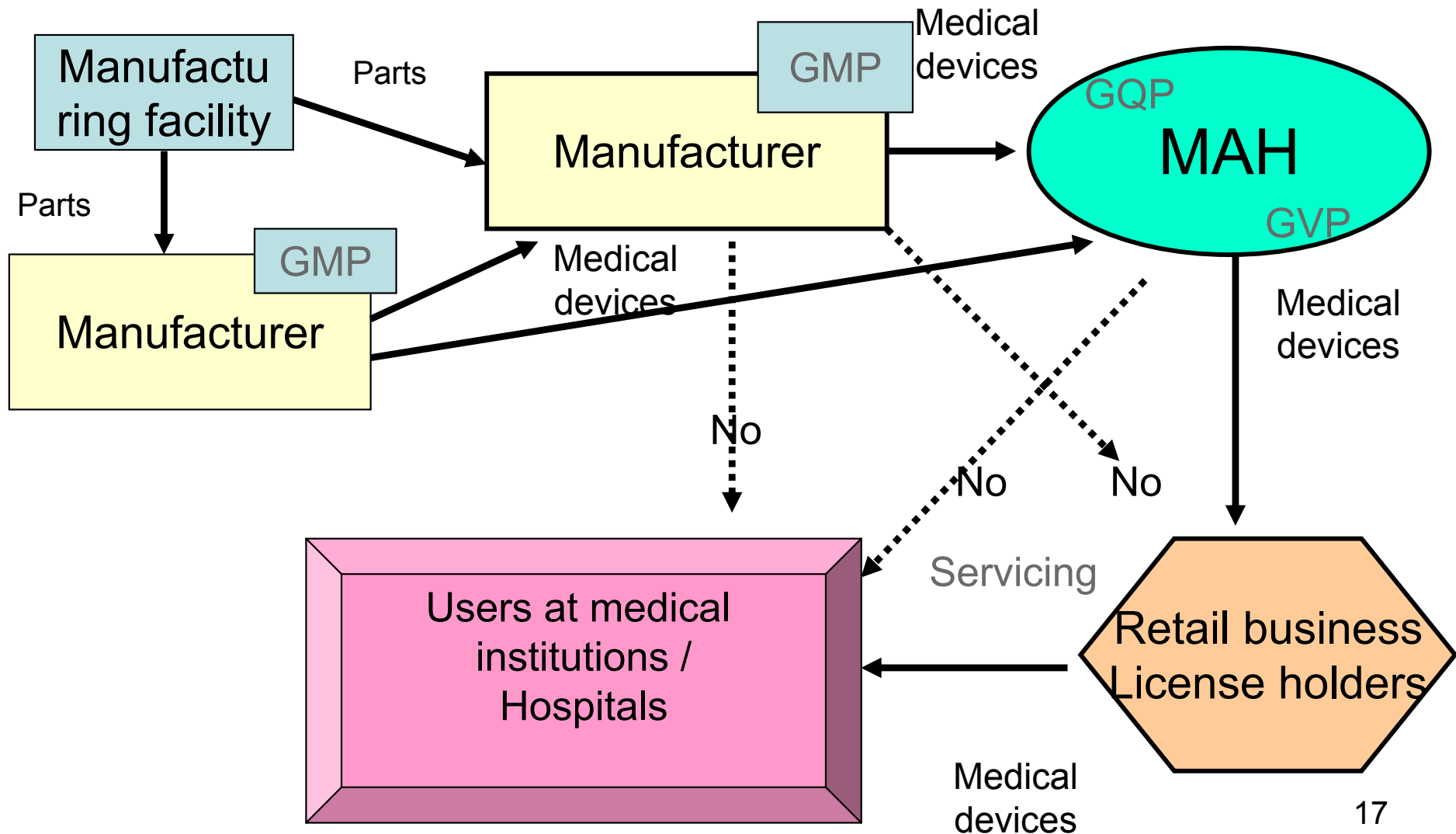


⑥ Follow-up audit (after certif.)



Marketing Authorization Holder (MAH)

Supply Flow of Medical devices and Regulatory Requirements



Japanese Pharmaceutical Affairs Law

Regulations in 2005

What's new ?

Current

“Who can apply device approval ?”

**Manufacturing Facility or importer of the device,
or foreign manufacturer may apply via ICC**

New

“Who can apply device approval ?”

“Marketing Authorization Holder” (MAH)

Japanese Pharmaceutical Affairs Law

Regulations in 2005

What's new ?

Current

“Foreign Manufacturer audited ?”

No. (Japanese importers are audited on its behalf)

New

“Foreign Manufacturer audited ?”

Yes, Foreign manufacturing facility must be registered, and audited

Japanese Pharmaceutical Affairs Law

Regulations in 2005

What's new ?

Current

“Who reviews the application ?”

Government

New

“Who reviews the application ?”

Government (MHLW and PMDA) for Class III & IV, and 3rd Parties for Class II devices

Japanese Pharmaceutical Affairs Law

If a foreign manufacturer hopes to export medical devices to Japan ...

Current

“What is necessary ?”

**Nominate an importer who has the importer’s license.
The importer or ICC applies for device approval.**

New

“What is necessary ?”

**Nominate a MAH in Japan who has the license.
MAH applies for pre-market device approval.**

Japanese Pharmaceutical Affairs Law

Who will be the Japanese 3rd Party Cert. Body ?

□ Expected Medical Devices 3rd Party Cert. Bodies

Total 17 companies submitted applications(end Nov.,04):including

**TUV Japan, JQA,
TUV Rheinland Japan,
UL-Apex, BSI Japan, JSA, JAMME,
and other certification bodies.**

Accreditation at the beginning Apr.,05

Japanese Pharmaceutical Affairs Law

Case study 2

There is a Medical Device Manufacturer in US which hopes to export Class III medical devices to Japanese market

-> What the company should do ?

- ❑ Nominate a MAH in Japan who must have the license for it
- ❑ Registration of the manufacturing facility
 - Requirements of infrastructure applied
- ❑ Obtain “SHONIN” (Device approval)
 - Pre-market application from the nominated MAH to PMDA
- ❑ Triggered by the submission of Pre-market application, a QMS audit will be conducted by Japanese PMDA at the foreign manufacturing facility