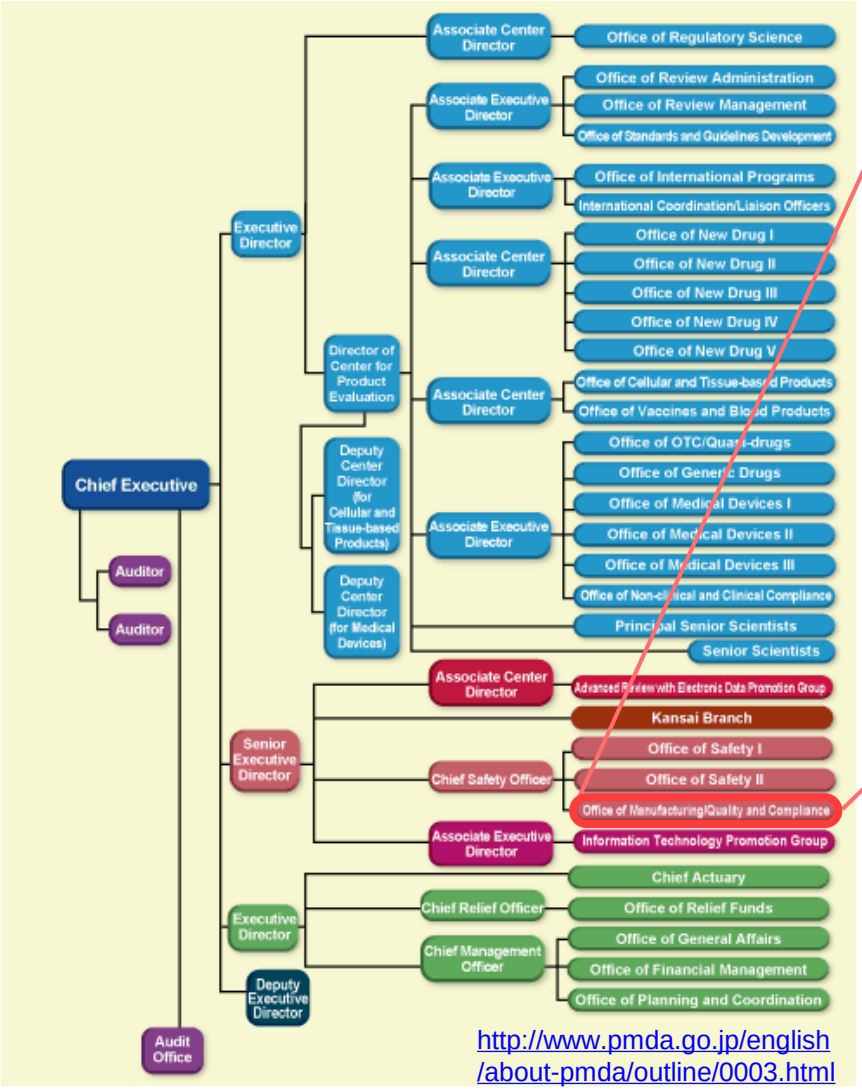
QMS regulation in Japan

Office of Manufacturing/Quality and Compliance

As of 1st April, 2015

Manufacturing/Quality and Compliance



http://www.pmda.go.jp/english/about-pmda/outline/0003.html

Manufacturing/Quality and Compliance

- QA of GMP/QMS
- GMP
- QMS
- RCB supervision

Main Topics

1. Definition

License, Registration, Approval

Marketing license

– a requirement for marketing any medical devices and IVDs in Japan.
Thus, all the marketing authorization holders (MAHs) shall have this license.

Manufacturing site registration (*"Toroku"*)

– a requirement for conducting specified manufacturing processes.
In the case of medical devices, design, main assembling, sterilization and domestic (Japan) distribution site shall be registered.

Marketing approval *("Shonin")*

– a requirement for any medical devices and IVDs marketed in Japan.
When applying for marketing approval of a new medical device or IVD or partial changes of authorized items hereto, QMS inspection application is also required.
The QMS inspection application is required every 5 years to maintain existing marketing approval.

Exceptional Marketing Authorization

Marketing Authorization Holder : MAH (“*Seihan*”)

A person who obtains the marketing license. MAH shall supervise and manage the manufacturer, and ensure the compliance with QMS of all manufacturing sites. Ensure proper product release to the market. MAH must be based in Japan.

Foreign restrictive authorization holder : FRAH

A foreign manufacturer who obtains the marketing approvals of medical devices in foreign country. FRAH may designate licensed MAH in Japan and have it market the product.

Designated MAH : DMAH (*“Sennin seihan”*)

MAH designated by FRAH to conduct required quality control duties inside Japan. FRAH shall have D-MAH take necessary measures for the prevention of occurrence of hazards to the public health and hygiene in Japan caused by the product.

MAH

- marketing authorization
- domestic quality control duties

FRAH + DMAH

- FRAH: marketing authorization
- DMAH: domestic quality control duties

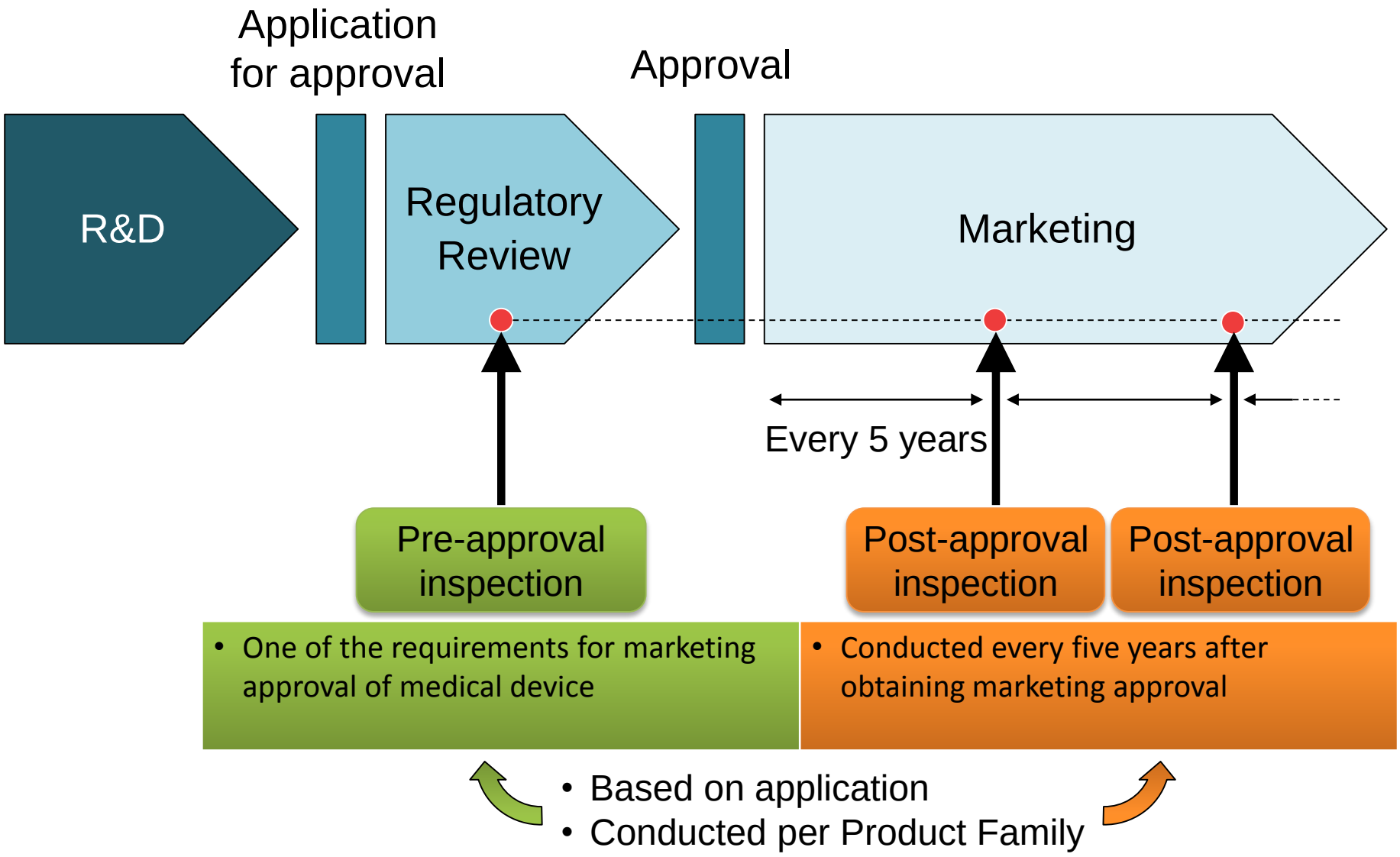
2. Overview of QMS Regulation Change

QMS regulation change under the revision of PAL

- Revised law went into effect in 25th Nov. 2014.
- Change of QMS inspection authority (see topic 3)
- Scope of Certification Standards will be expanded (see topic 3)
- Manufacturer's License and Accreditation to Registration (see topic 4)
- Revision of QMS Ordinance
  - QMS inspection per product family (see topic 4)
  - 2nd Chapter became harmonized to ISO13485 (see topic 5)
  - QMS inspection applied to Market Authorization Holder (MAH) (see topic 5.1)

3. Type of QMS Inspection

QMS Inspections



Type of QMS Inspection

1. Pre-approval inspection

Required before the marketing approval.

2. Pre-partial change approval inspection

Required before the partial change approval.
Inspection scope is MAH and the change-related sites.

3. Periodic post-approval inspection

Required for maintaining marketing approval every 5 years since the initial marketing approval.

4. Additional inspection

Required for the notified cases. ex) specialized inspection for biological products, micro machine and medical devices utilizing nano-materials etc..

QMS Inspection Authority

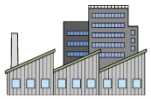
Product		Inspection Authority
Medical Devices	• Class IV • New medical devices • Cell / Tissue-based medical devices • Class III and Class II (without CS*)	PMDA
	• Class III and Class II (with CS*)	Registered certification body
IVDs	• New drugs • Radioactive drugs • Products without CS*	PMDA
	• Products with CS*	Registered certification body

*CS : Certification Standards

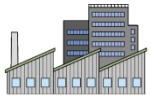
4. Scope of mfg. site registration QMS inspection

Manufacturing site Registration

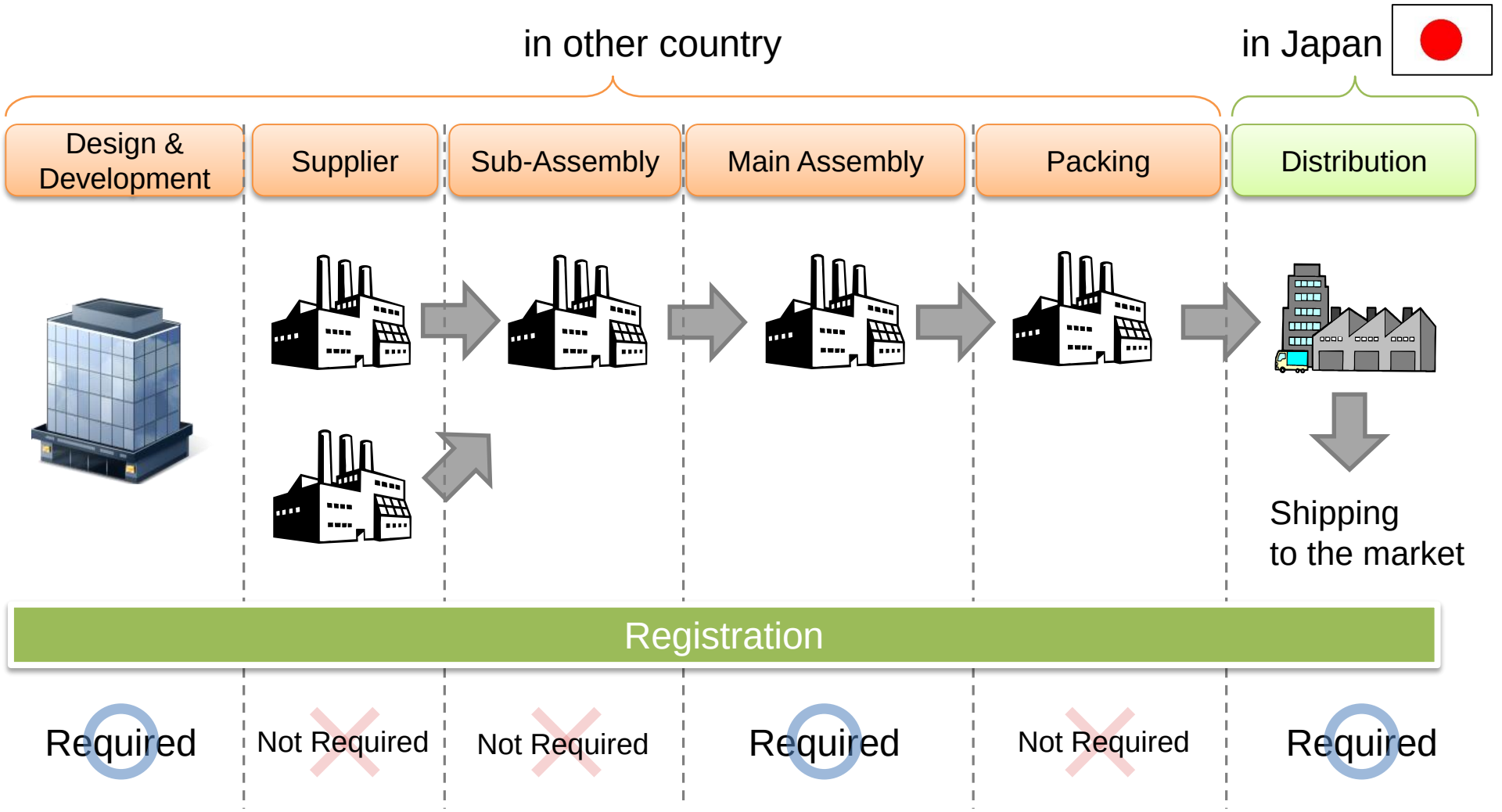
Sites listed below are required to register for each products.

Site	Definition
 Design Facility	(1) maintain records of design and development, and (2) the responsible person should work here
 Main Assembling Plant	(1) mainly responsible for QMS or product realization of the products, and (2) implement assembling(filling) processes.
 Sterilizer	(1) implement sterilization process
 Domestic (Japan) Distribution Center	(1) Storage and final release of the products to Japanese market.

Scope of Registration and Inspection

	Registration	QMS Inspection
 MAH Marketing Authorization Holder	N/A The license of marketing is required	○ Required
 Design Facility	○ Required	○ Required
 Main Assembling Plant	○ Required	○ Required
 Sterilizer	○ Required only for sterile medical device	○ Required only for sterile medical device
 Domestic (Japan) Distribution Center	○ Required	○ Required
 Other sites	× Not Required	△ Depends PMDA determines based on risk assessment

Example of mfg. site registration



Registration of Manufacturer

[Before Revision] License, Accreditation → [After Revision] Registration

Manufacturer needs “Registration” before the QMS inspection is conducted.

License and Accreditation of manufacturer changed to Registration.

BFR(Buildings and Facilities Regulation) conformity was one of the prerequisites for License and Accreditation, but now NOT for Registration.

	Before Revision	After Revision
Licensing system	License (Domestic) Accreditation (Foreign)	Registration (Domestic, Foreign)
Authority to provide license	Prefecture (Domestic) MHLW (Biological, Foreign)	Prefecture (Domestic) MHLW (Foreign)
Category	General, Sterilization, Biological, Packaging.	None
Requirements for licensing	Reasons for disqualification (Health, Crime, Revocation)	Reasons for disqualification (Health, Crime, Revocation)
	Facilities requirement	None

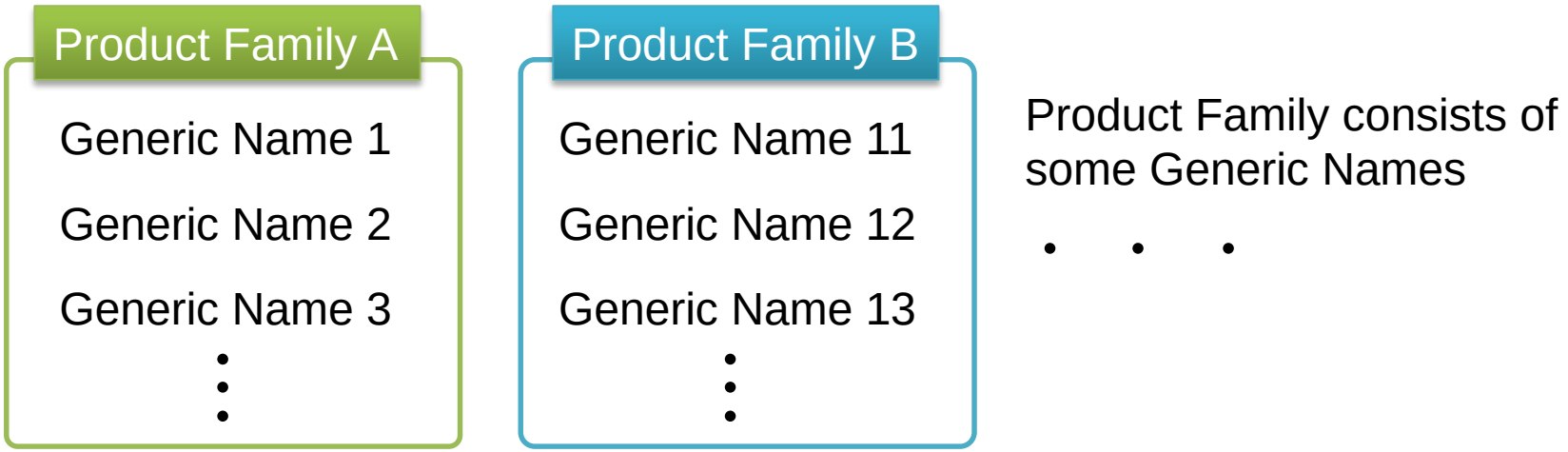
Application Materials for Registration

- Application for Registration (Form No.63-5)
- Document that states an applicant is not intoxicated person
- Curriculum vitae of the representative in the facility
- Registered premises and/or areas with drawings and/or bird's eye-views

Product Families

QMS inspection is conducted per **“Product Family”**

- Generic names of Medical Devices and IVDs are grouped into **“Product Families”** depending on factors such as mfg. process, characteristics, usage method, risk etc..



- The relationship between product family and generic name will be announced by notification [1]

Exception of Product Families

However…

- Products having generic names not grouped into product family: QMS inspection per generic name
- High risk product: QMS inspection per product (specified in public notice [2])

QMS Inspection is conducted per…

Medical Devices and In-Vitro Diagnostics（Class II～IV）

- per Product (High risk Product)
- per Generic name (not grouped into product family)
- **per Product Family**

Product Families

Product Families: Class IV

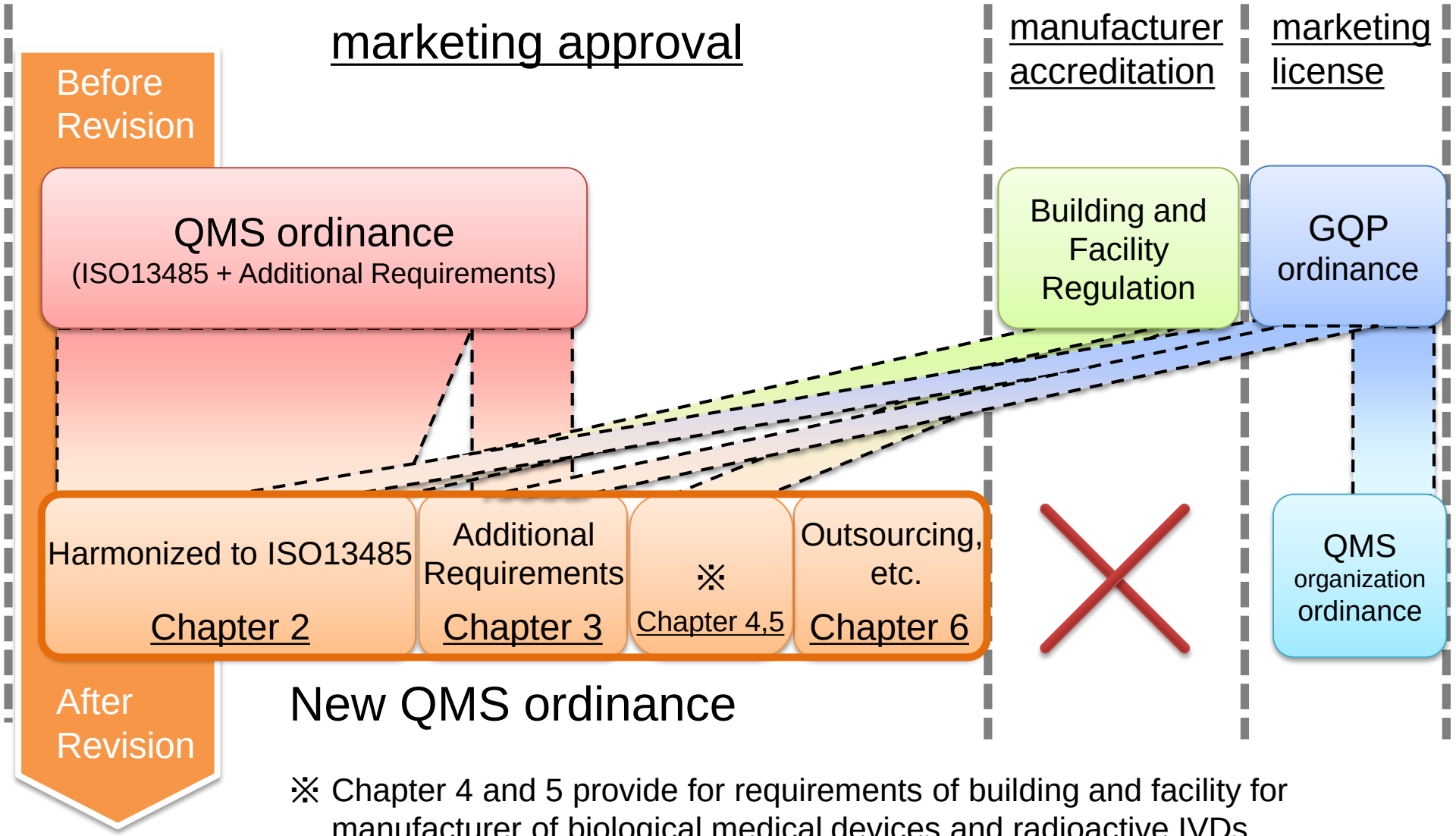
- Class IV Product Family is established by Japanese original definition.
- Examples of product families:
  Stent
  Stent graft
  Active catheter
  Cardiac pacemaker and defibrillator
  Ventricular assist device

Product Families: Class II / III

- Class II / III Product Family refer to NBOG BPG 2009-3.
- Examples of product families:
  Non-active instruments (MD 0106)
  Non-active cardiovascular implants (MD 0201)
  Non-active dental equipment and instruments (MD 0401)
  Devices for stimulation or inhibition (MD 1103)
  Imaging devices utilizing ionizing radiation (MD 1201)

5. QMS Inspection

Revision of QMS Ordinance

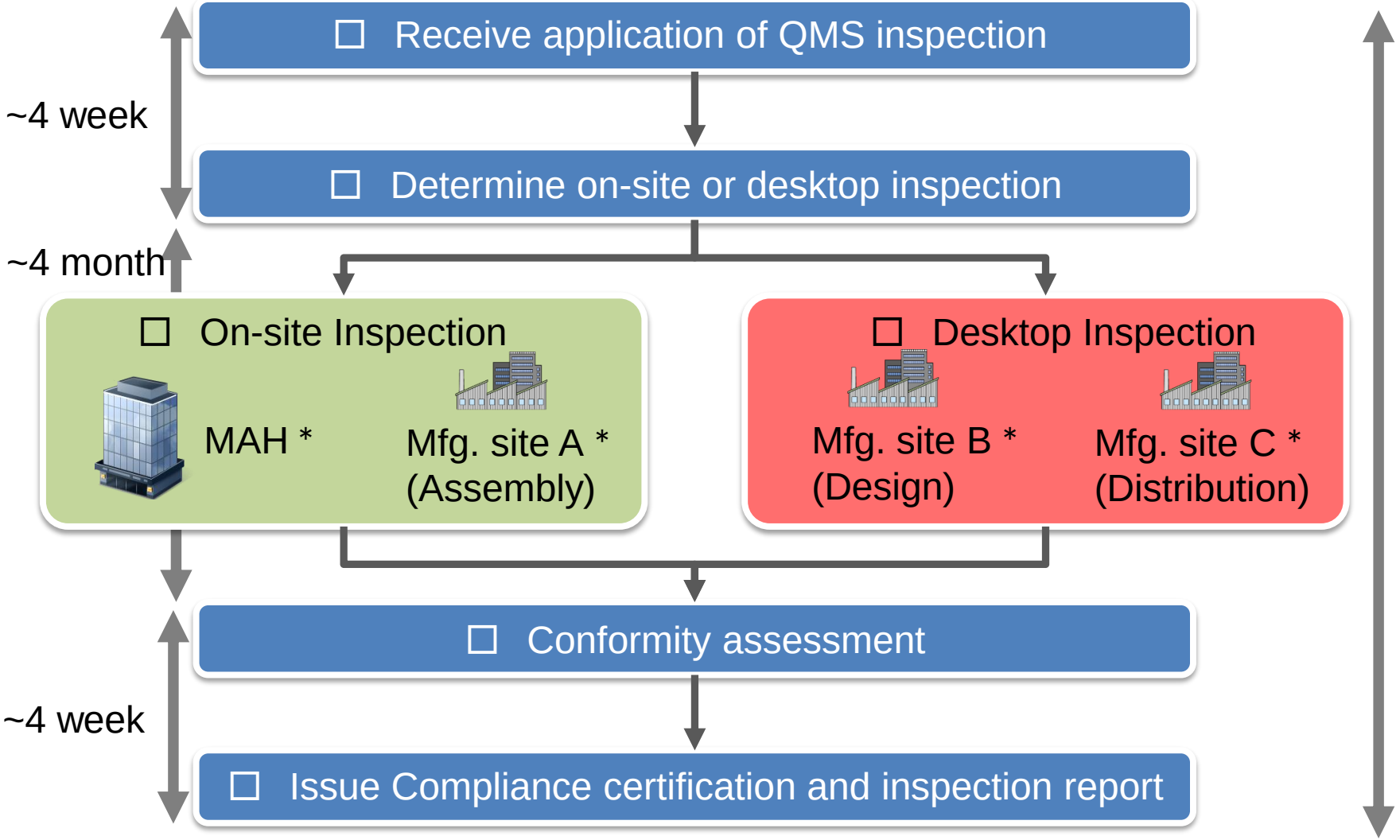


※ Chapter 4 and 5 provide for requirements of building and facility for manufacturer of biological medical devices and radioactive IVDs.

Contents of New QMS ordinance

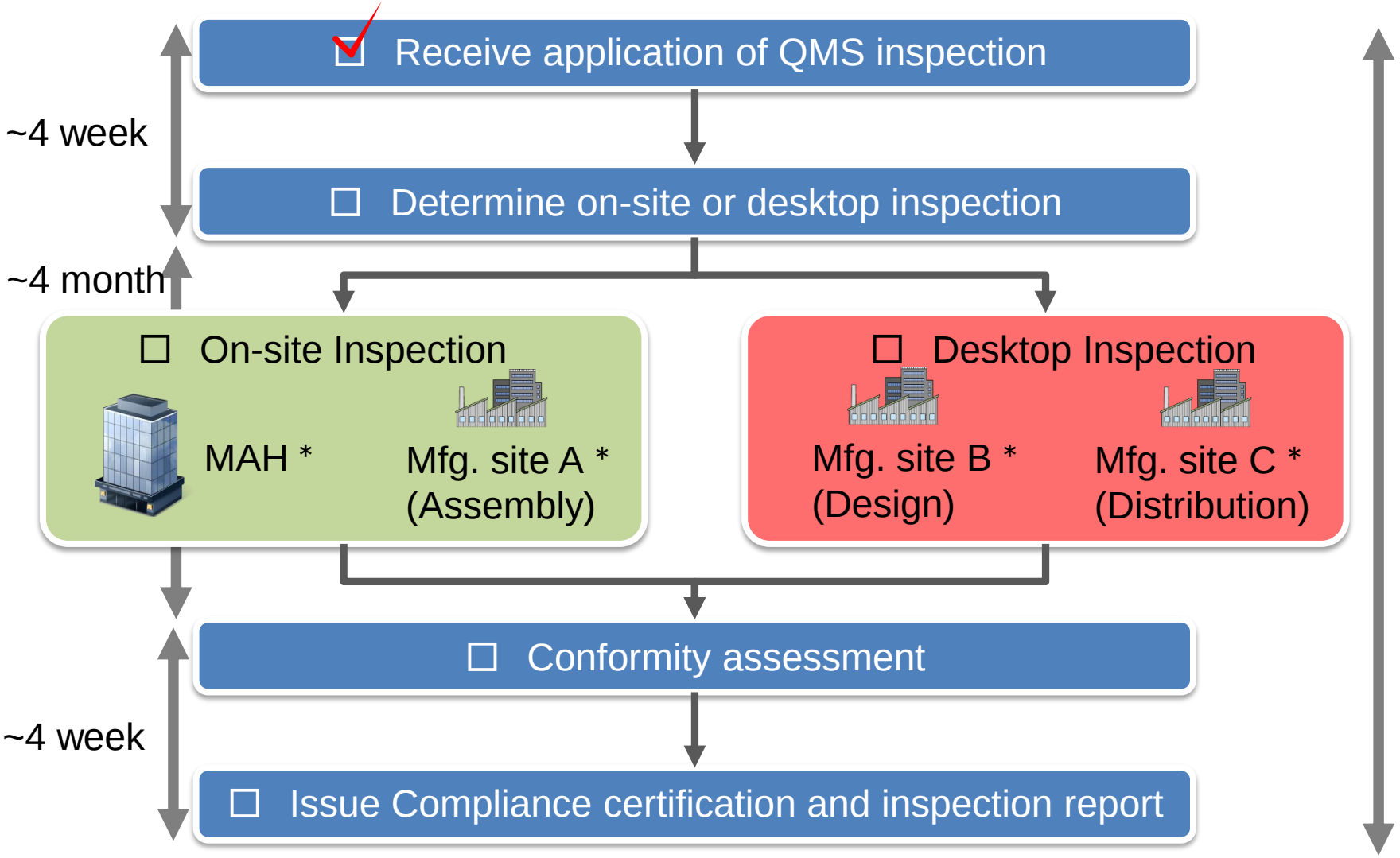
Chapter	Title	Article
1	General Provisions	1~3
2	Medical Devices Manufacturing Harmonized to ISO13485:2003	4~64
3	Additional Requirements.	65~72-3
4	Biological-origin Medical Device, etc. Manufacturers (Domestic, Foreign) Additional requirements according to the characteristics of the products	73~79
5	In-Vitro Diagnostic Radioactive Reagents Manufacturers(Domestic, Foreign) Additional requirements according to the characteristics of the products	80~81
6	Provisions Applied *Mutatis Mutandis* of Medical Device, etc. Manufacturing Sites, etc.	82~84

Overview of QMS inspection flow



*: Example. PMDA determines whether on-site or desktop inspection based on risk assessment. See 5.2..

Overview of QMS inspection flow

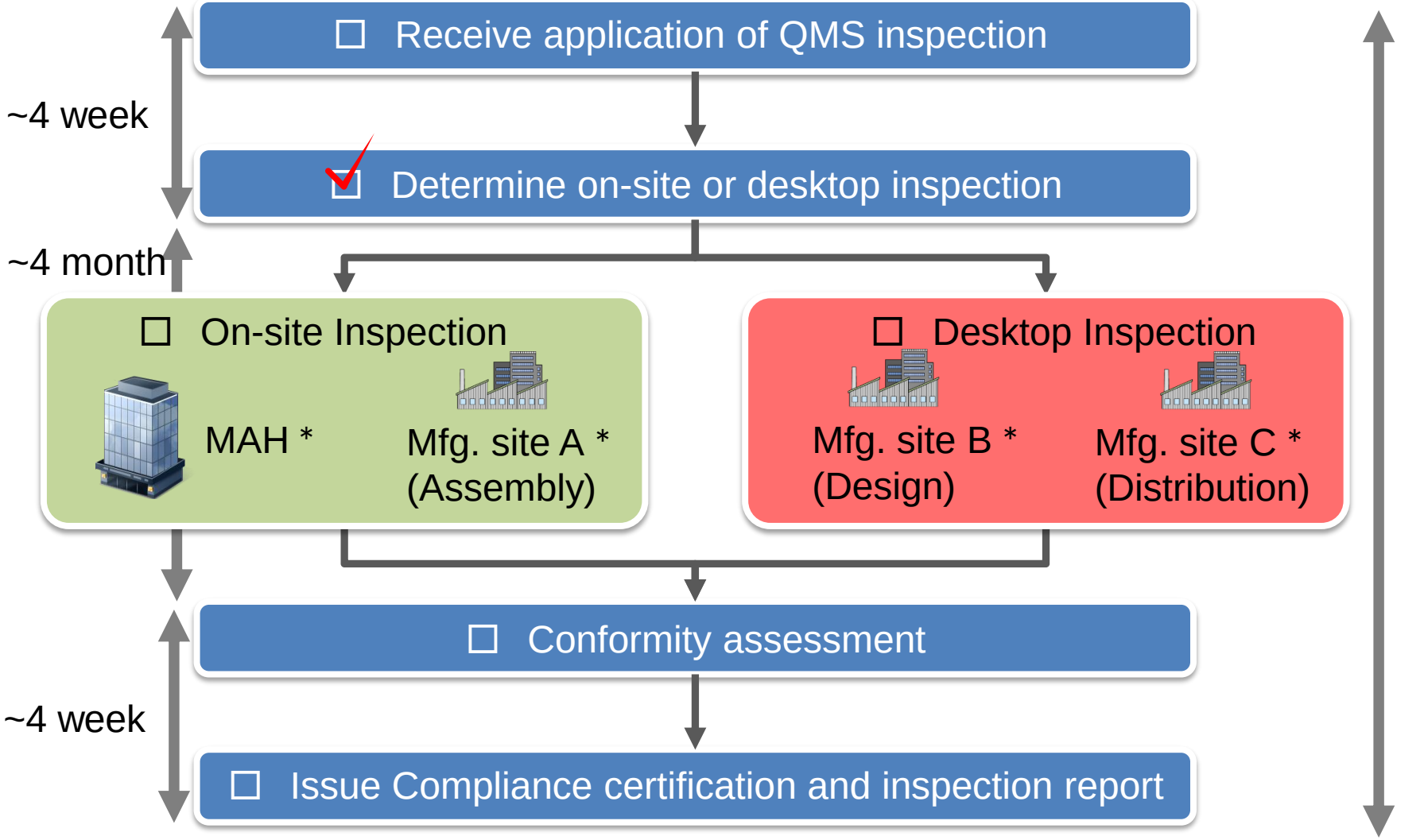


*: Example. PMDA determines whether on-site or desktop inspection based on risk assessment. See 5.2..

Documents for QMS application

No.	Documents	Scope	Pre-Approval/ Pre-Partial	Post-approval
1	ISO13485 Certification, registered certification body's Inspection report, etc	Mfg. sites	Required	Required
2	Manufacturing process flow	Product subject to inspection	Required	Required
3	Outline of content of mfg. site's activities and documents which can identify mutual relations of QMS between MAH and mfg. sites.	Mfg. sites	Required	Required
4	Outline of mfg. site	Mfg. sites	Required	Required
5	Product list for application	Product family	Required	Required

Overview of QMS inspection flow



*: Example. PMDA determines whether on-site or desktop inspection based on risk assessment. See 5.2..

Decision of desktop or on-site

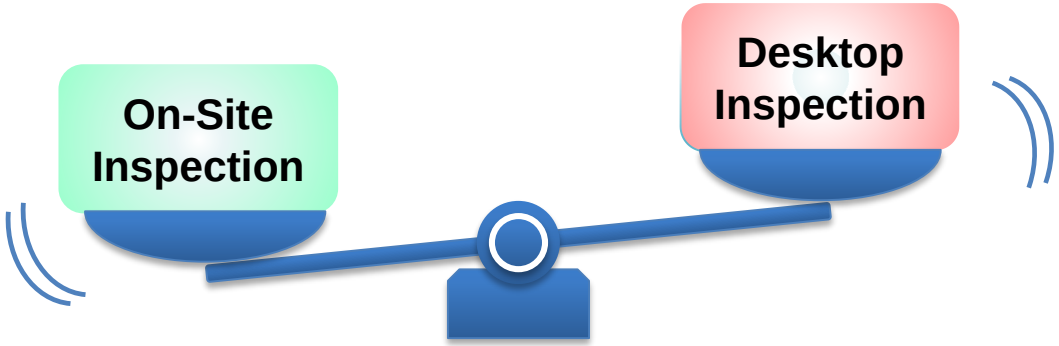
Input Information

- Submitted documents
- Reported adverse events and recalls
- Records of previous QMS inspections etc.

Risk Assessment

- Complexity of manufacturing processes
- Risk associated with the use of products
- Previous nonconformities and recalls
- Results of the previous on-site inspections
- Certificate of ISO13485 etc.

Decision of on-site or desktop



High possibility of desktop inspection

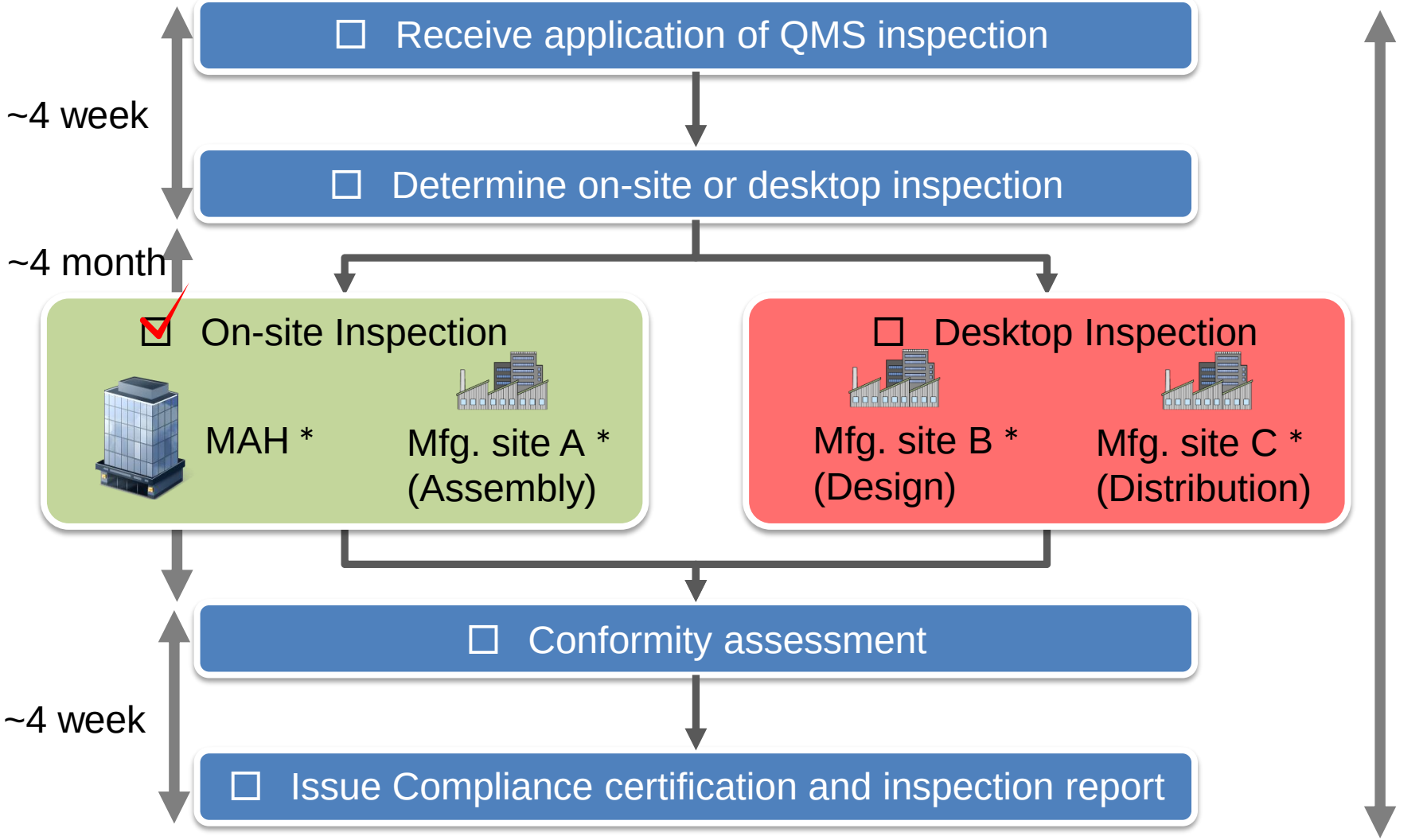
If MAH or Mfg. sites have…

(1) Latest ISO13485 certification or audit report within 3 years of issue.
issued by certification bodies registered under the medical device regulation system of Japan, US, Europe, Australia or Canada.

(2) Latest On-site QMS inspection report within 3 years of issue by registered certification bodies in Japan

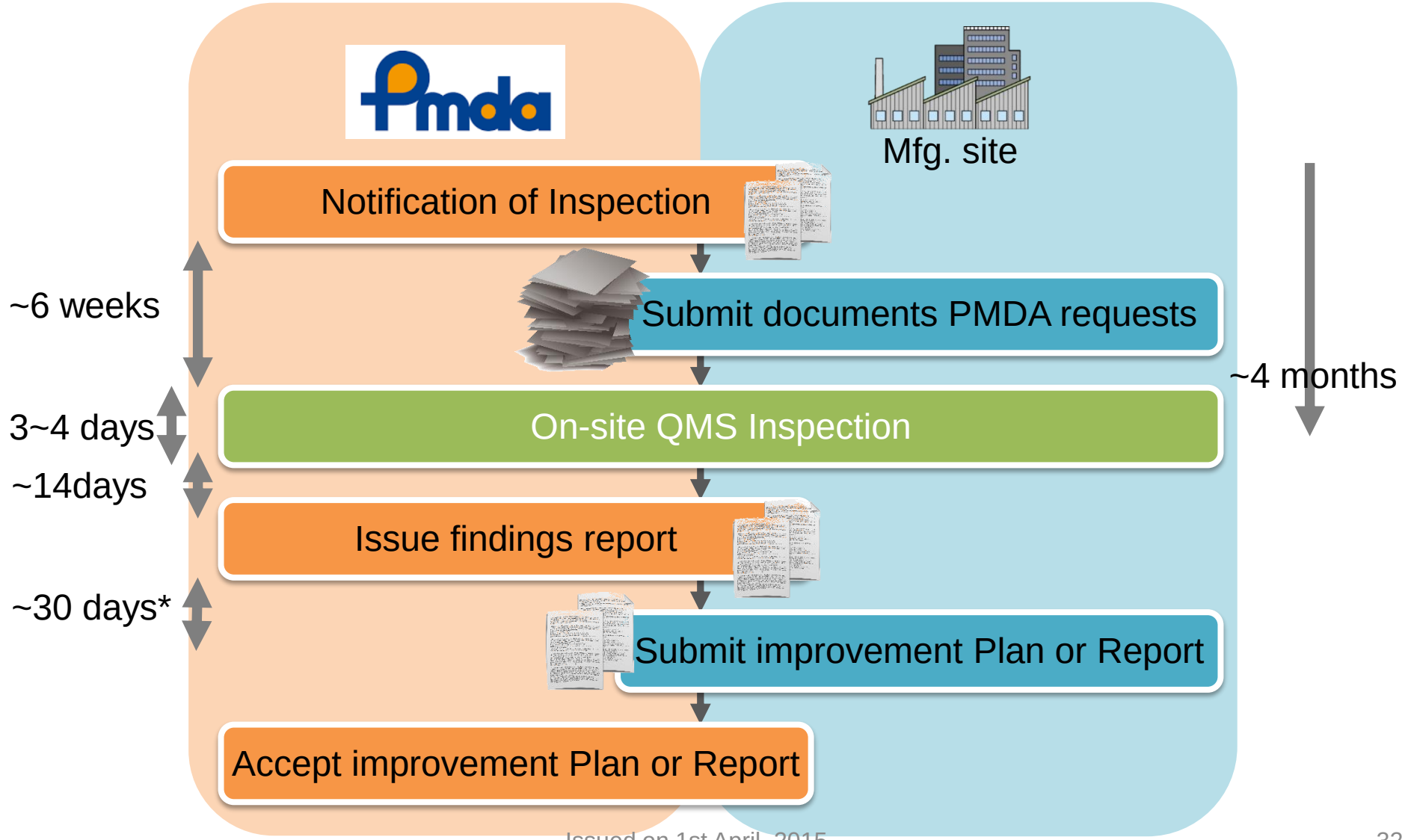
(3) QMS inspection report issued by the foreign governments under MOU, etc.

Overview of QMS inspection flow



*: Example. PMDA determines whether on-site or desktop inspection based on risk assessment. See 5.2..

On-site inspection flow chart



Overseas on-site inspection

- 2 inspectors / inspection in general
- Accompanied by interpreters
- Duration : 2 to 4 days
- Notification : ~ 6 weeks before the inspection
- Scope : Product Family
  (Not only application product, but also products in same product family are subject to QMS Inspection.)
- Request for documents prior to the inspection

Example of QMS Inspection Schedule

Date	Time	Item
Day 1	9:00~12:00	1.Opening meeting (1) Introduction of Inspection (2) Overview of Company and Facility* (3) Overview of Products* (4) Changes (QMS) from the last Inspection* 2. Management (1) QMS organization (including Agreement made with MAH (2) Quality Manual (3) Quality Policy and Objectives (4) Management Review 3. Documentation and Records
	13:00~17:00	4. Plant tour
Day 2	9:00~12:00	5. Product and Process controls 6. Product documentation (Seihin Hyojun Syo)
	13:00~17:00	7. Design and Development (including Risk Management)
Day 3	9:00~12:00	8. Purchasing Control 9. Customer related processes
	13:00~17:00	10. Corrective and Preventive Actions 11. Teem Meeting of Inspectors 12. Confirmation on Findings 13. Closing Meeting

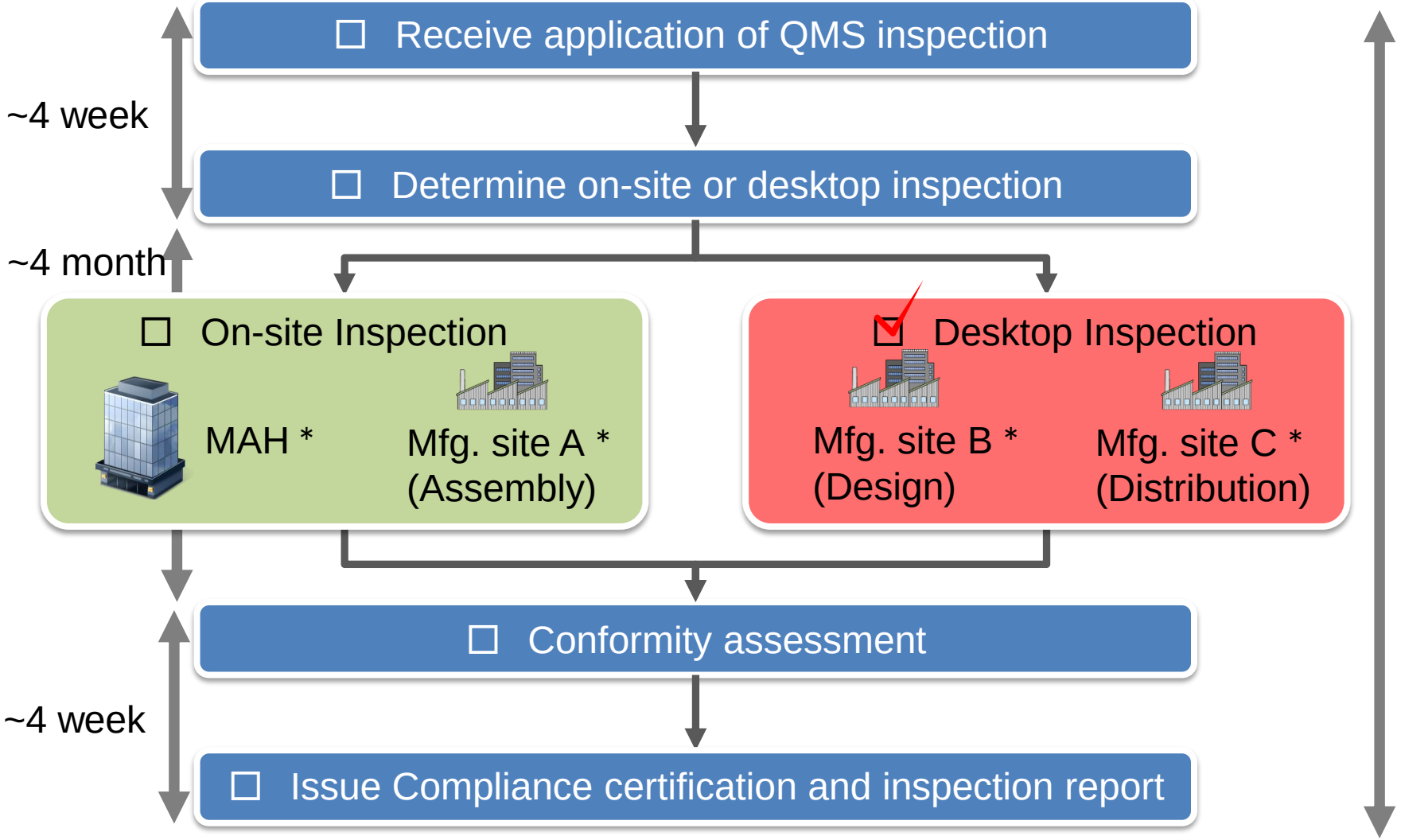
As to items with*, Please give presentations to Inspectors.
Note that this schedule may slightly change due to progress.

Documents to be submitted for on-site inspection

Request for Submitted Documents for On-site Inspection (ex)
・Quality Manual
・List of QMS documents
・Quality control process chart
・CAPA log
・・・・・・・・・

in English or Japanese

Overview of QMS inspection flow



*: Example. PMDA determines whether on-site or desktop inspection based on risk assessment. See 5.2..

Documents for QMS desktop review

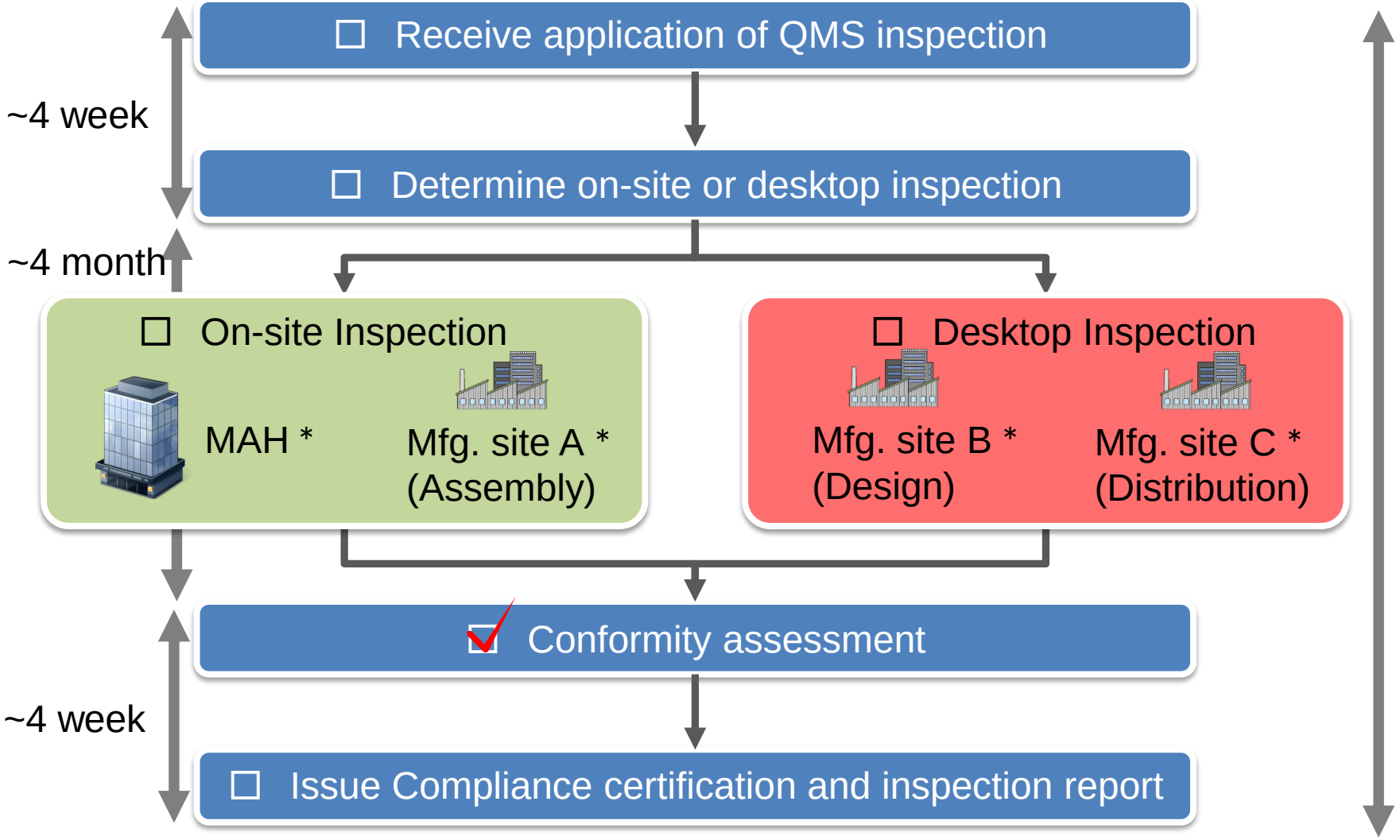
	Documents	Outline of Documents	Subject	Pre-/ Pre-partial	Post-approval
Documents about subject of QMS Inspection mfg. site	Layout of all mfg. site building	・Aerial photograph or location map of mfg. site	Mfg. sites (expect for Design facility)	required	required
	Floor plan	・Clean room grade ・Differential pressure ・List or layout of representative manufacturing and inspection equipments	Mfg. sites (expect for Design facility)	required	required
	Organization chart	・Responsible persons and departments related to QMS	Mfg. sites	required	Required
Documents about QMS	Quality management system	・Quality Manual	Mfg. sites	required	required
	List of documents identified with QMS	・Including name, number, and retention period of QMS control documents	Mfg. sites	required	Required
Documents about product subject to the Inspection	*Seihin Hyojun Sho*	・Seihin Hyojun Syo is document which showed the location of documents required by QMS.(Device master record OK) ・Reference：Aug27, 2014 PFSB/CND No.0827-2	Product subject to Inspection	required	required
	Validation status of mfg. process	・List showing mfg process , mfg. site, and date about the validation.	Product subject to Inspection	required	required

Cases from desktop to on-site inspection

We may change desktop inspection to on-site inspection in the following cases as needed.

- ✓ If there is no response or the response is not satisfactory
- ✓ The documents are not in order, and haven't improved

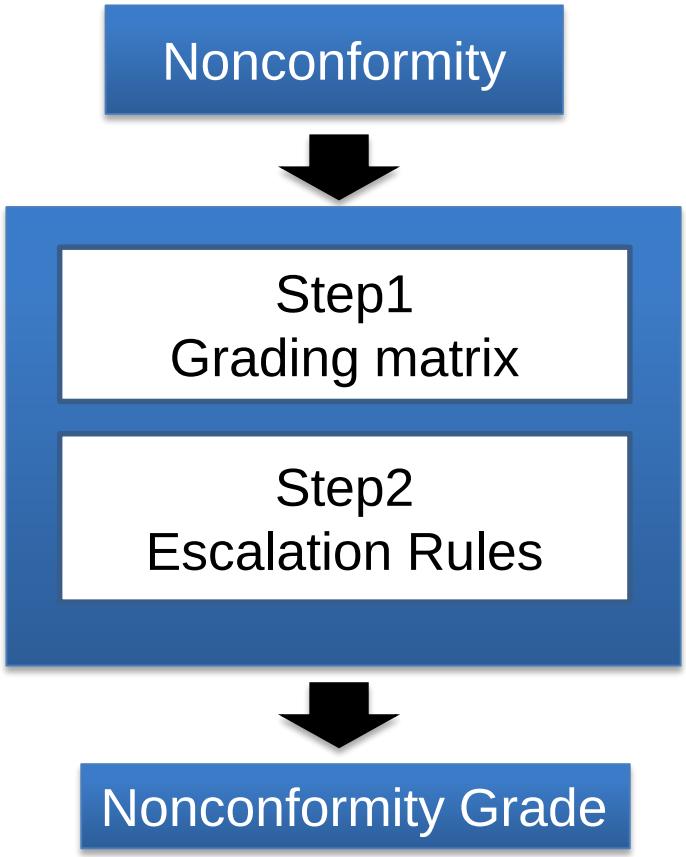
Overview of QMS inspection flow



*: Example. PMDA determines whether on-site or desktop inspection based on risk assessment. See 5.2..

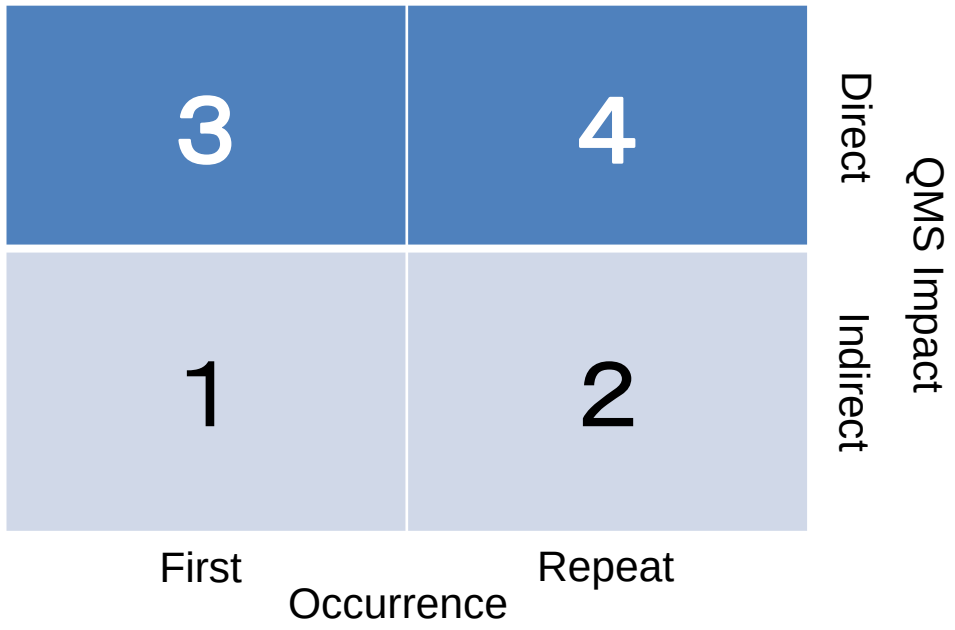
Grading of Nonconformities

Figure 1:Grading overview



Reference：GHTF/SG3/N19:2012

Figure 2:Grading matrix



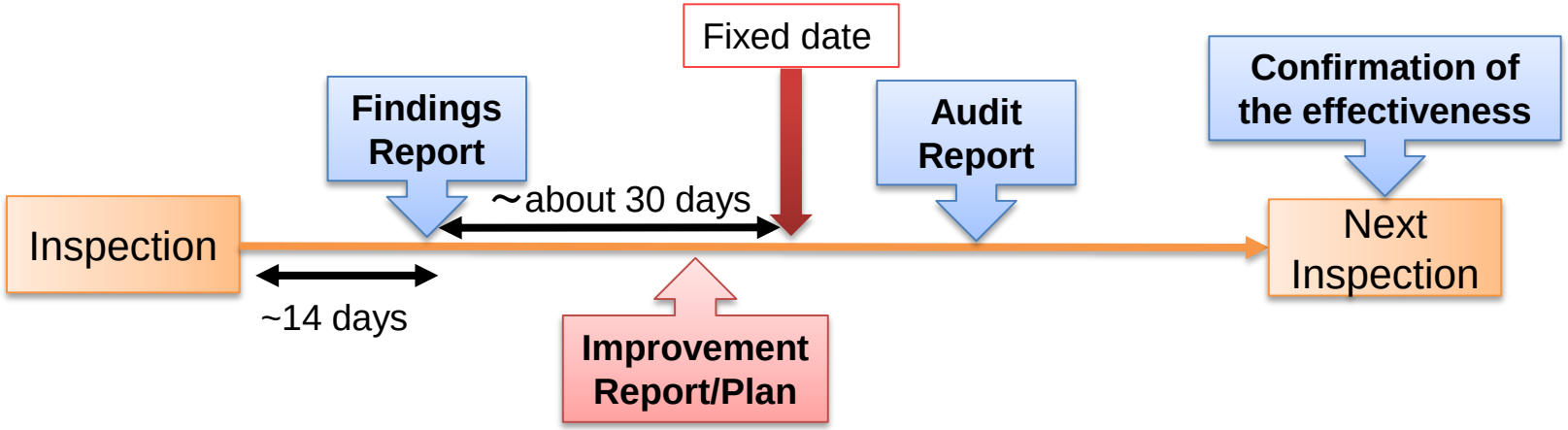
Direct QMS Impact
Article 25 to 65, 69, 72, 73, 75, 76, 80, 81, 84

Indirect QMS Impact
Article 5 to 24, 66 to 68, 70, 71, 72-2, 74, 77 to 79

QMS compliance evaluation(1/2)

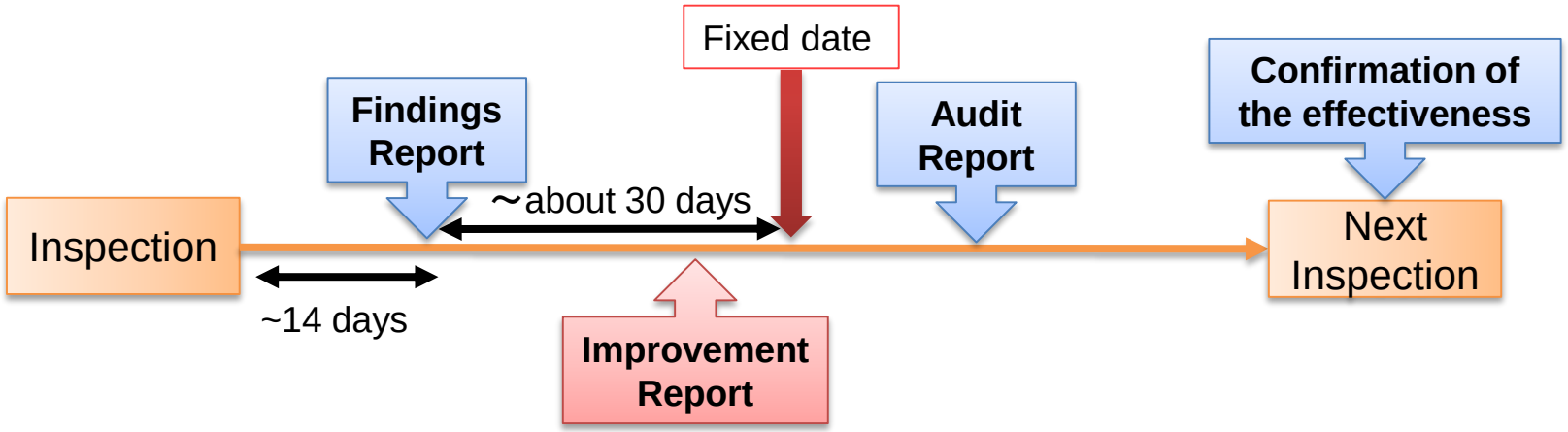
Only Grade 1

Evaluation：Conformity

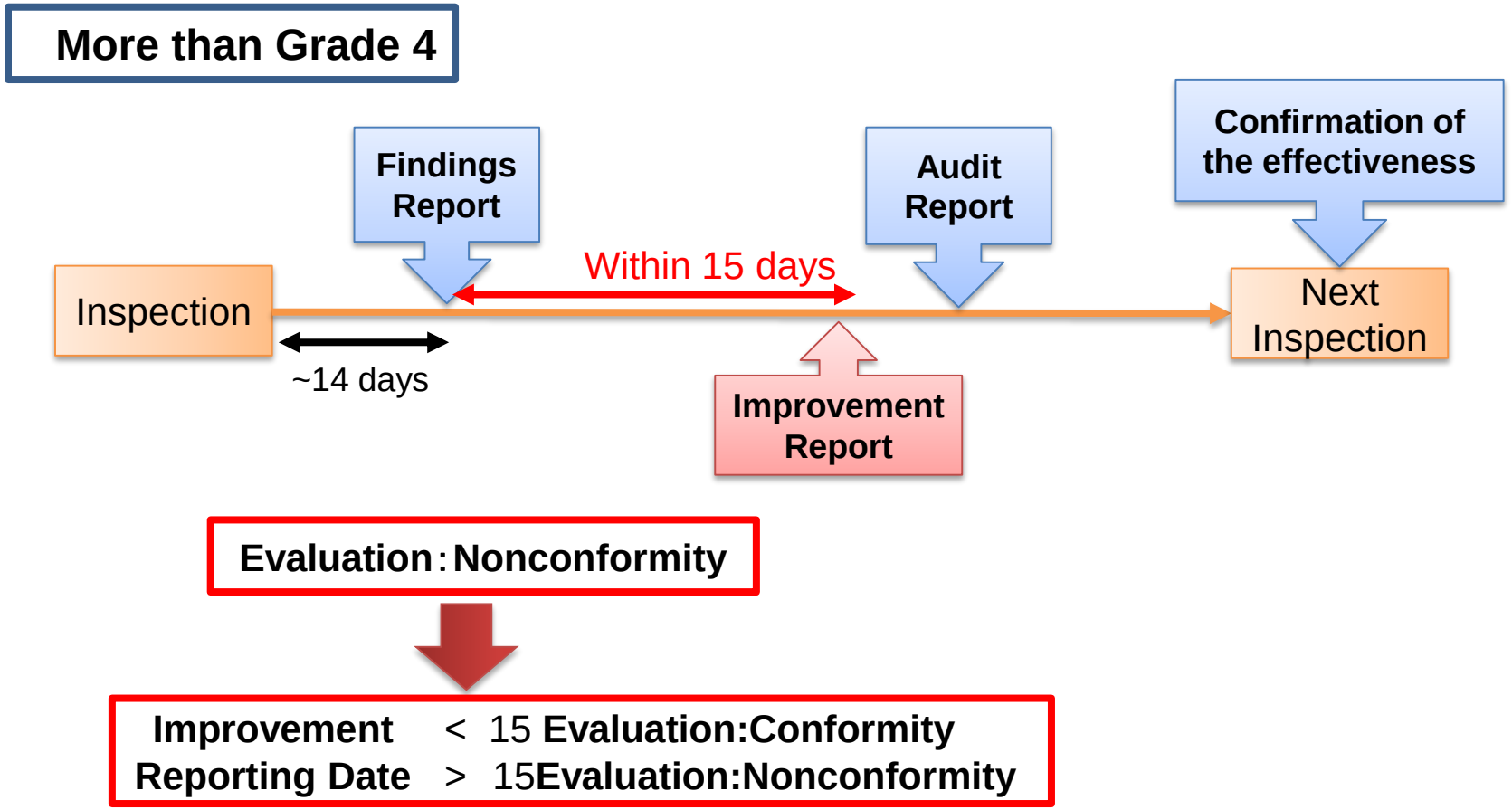


Grade 2, 3

Improvement Reporting Date	<	Fixed date	**Evaluation:Conformity**
	>	Fixed date	**Evaluation:Nonconformity**

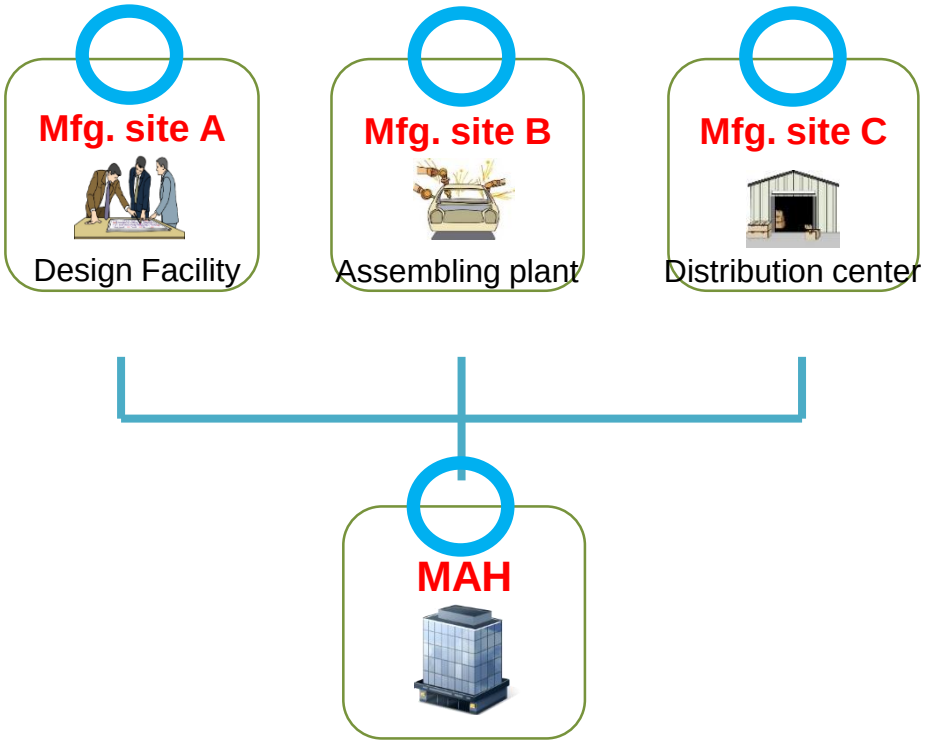


QMS compliance evaluation(2/2)



Final assessment

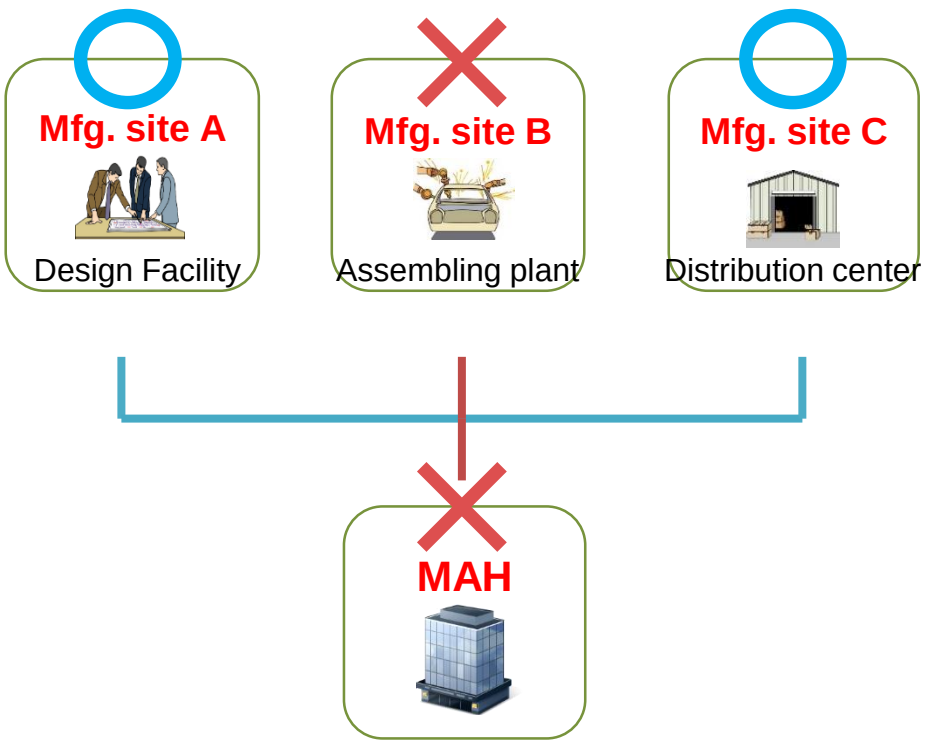
If all sites are conformity…



Conformity for application

conformity
nonconformity

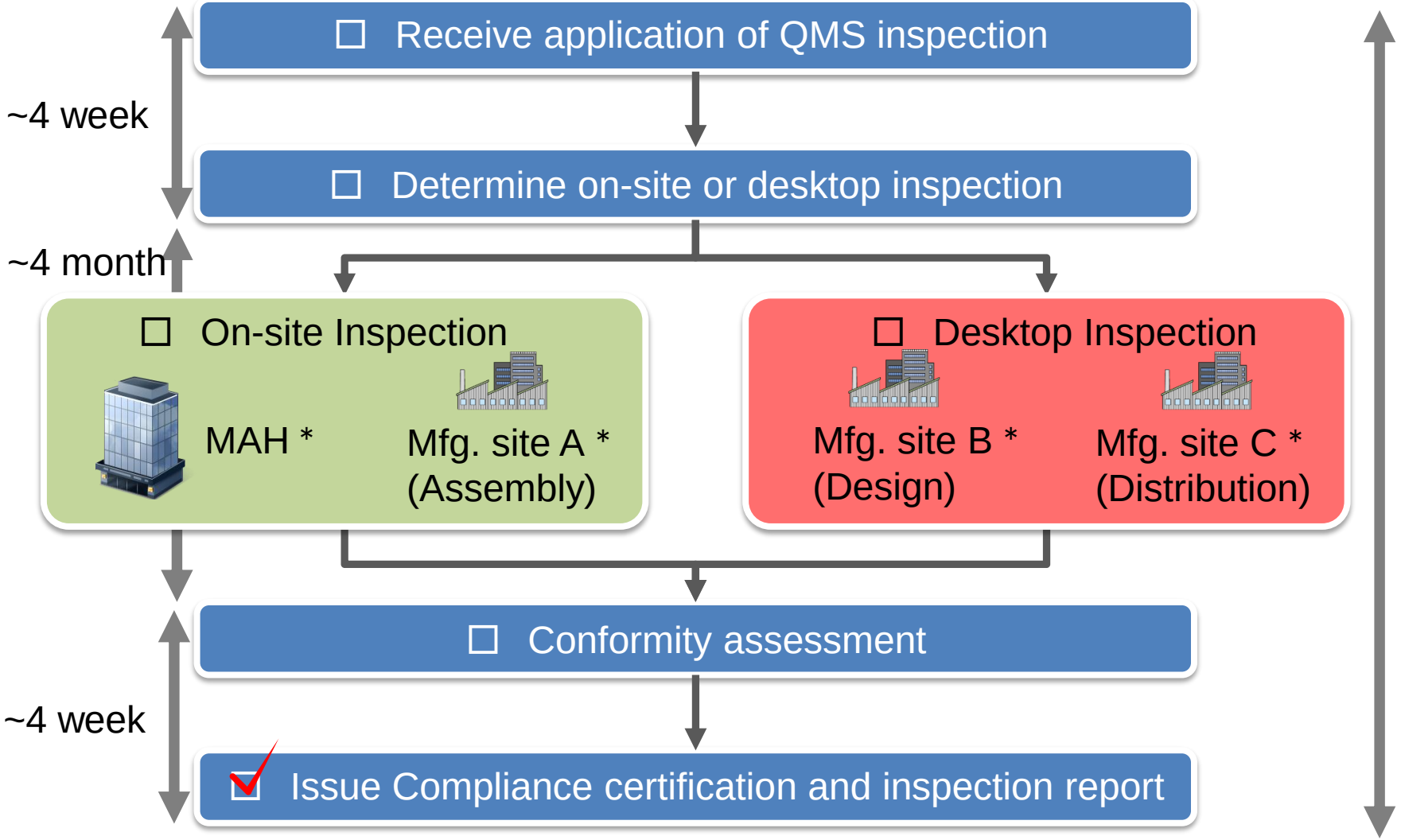
If mfg. site B is nonconformity…



MAH is nonconformity, too.
(Reference: QMS ordinance article 65)

Nonconformity for application

Overview of QMS inspection flow



*: Example. PMDA determines whether on-site or desktop inspection based on risk assessment. See 5.2..

QMS Compliance Certification

QMS Compliance Certification

Summary Report

Marketing Authorization Holder

On-site Inspection

Inspection Report

Manufacturing Site
（Design Facility）

Desktop Inspection

Assembling Plant

Manufacturing Site
（Assembling Plant）

On-site Inspection

Inspection Report*

*Send to MAH, in a general.

Manufacturing Site
（Contract Sterilizer）

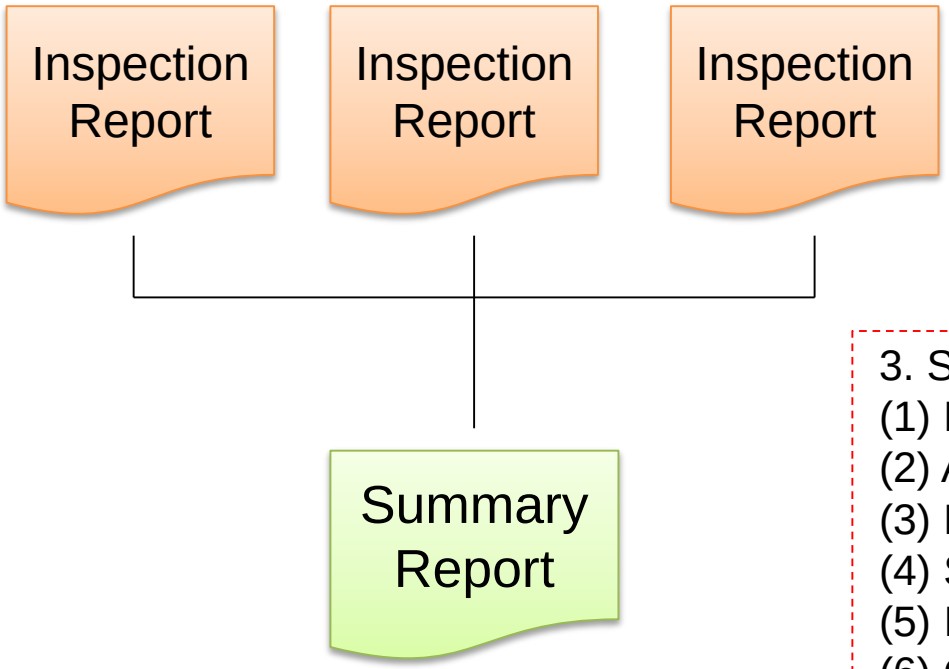
Desktop Inspection

Manufacturing Site
（Domestic Distribution Center）

Desktop Inspection

Issued on 1st April, 2015.

Summary Report



Reporting Date:

QMS summary report

[Inspecting organization]

Lead inspector:

Inspector:

1. Reference No.

2. General Information

(1) Name of the MAH

(2) Address of the MAH

(3) Products under the inspection

(4) Purpose of the inspection

3. Summary of result of each mfg. sites

(1) Name of the mfg. site

(2) Address of the mfg. site

(3) Registration number and date

(4) Sub-systems under the inspection

(5) Inspecting date

(6) On-site or desktop

(7) Reference no. of QMS inspection report

(8) Result of the inspection

4. Total result

5. Recital

References

References

[1] MHLW Compliance and Narcotics Division on September 11, 2014 as notification No. 5

[2] MHLW on August 6, 2014 as Notice 317

QMS regulation-related sites

PMDA / QMS (English)

http://www.pmda.go.jp/english/review-services/gmp-qms-gctp/0002.html

PMDA / Notifications related to PAL Revision (Japanese)

http://www.pmda.go.jp/review-services/drug-reviews/about-reviews/devices/8077.html

MHLW (English)

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