

Risk based approaches in the Japan-GMP Regulation

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Agenda

- 1. Overview of GMP inspectorates in Japan**
- 2. Application of Risk Assessment: On-site or Desktop inspection**
- 3. Application of Risk Based Approaches on GMP inspections**
- 4. Application of Risk Management: In case of Recall**
- 5. Future issues**

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GMP inspection authorities

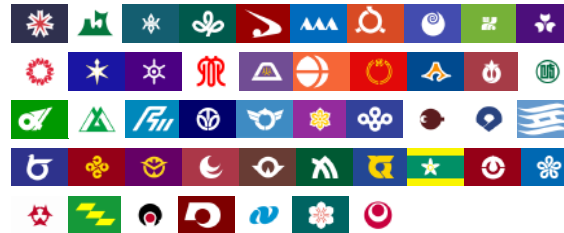
- **MHLW**



- **PMDA**



- **47 Prefectures**



Hokkaido, Aomori, Akita, Yamagata, Iwate, Miyagi, Fukushima, Tochigi, Gunma, Ibaraki, Saitama, Chiba, Tokyo, Kanagawa, Niigata, Nagano, Yamanashi, Shizuoka, Aichi, Gifu, Toyama, Ishikawa, Mie, Fukui, Shiga, Nara, Wakayama, Kyoto, Osaka, Hyogo, Tottori, Shimane, Okayama, Hiroshima, Yamaguchi, Tokushima, Kagawa, Kochi, Ehime, Fukuoka, Oita, Miyazaki, Saga, Nagasaki, Kumamoto, Kagoshima and Okinawa.

GMP inspection authorities



GMP Inspection Manual

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

- **Control inspectorates**
- **Ultimate responsibility**

Delegate MHLW's authorities by Law/Ordinance

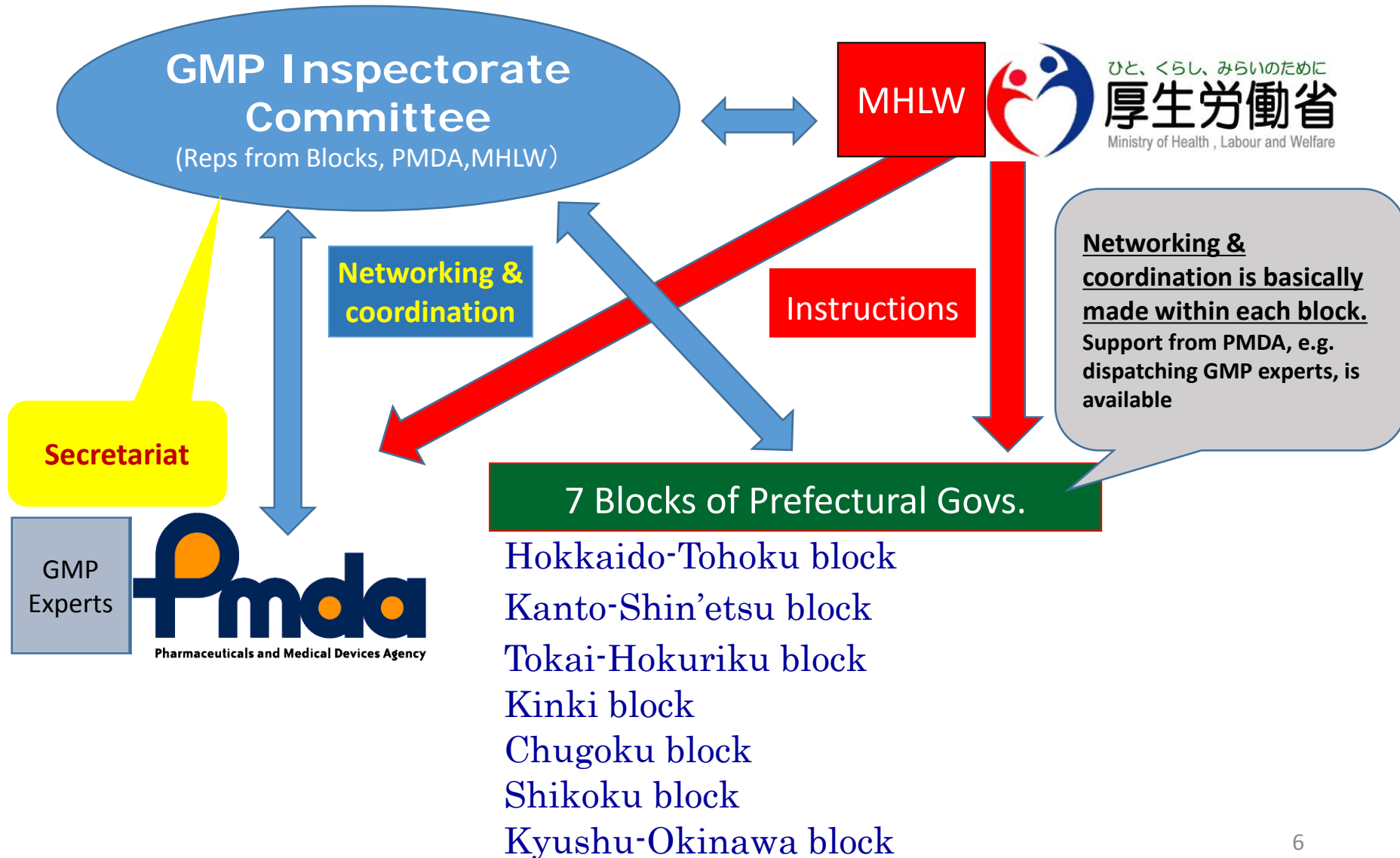


Prefectures
(47 Inspectorates)




PMDA is partially vested with authorities of MHLW (assessment, GMP inspection, information gathering)

Prefectures are delegated with part of MHLW's authorities for their administrative jurisdictions

GMP inspectorate committee

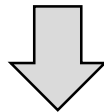


Authorities of GMP inspection

	Domestic Site	Foreign Site
New Drugs, Biological Products, Radio Pharmaceuticals	 <p>Pharmaceuticals and Medical Devices Agency</p>	 <p>Pharmaceuticals and Medical Devices Agency</p>
Other Drugs	47 Pref. Gov.	 <p>Pharmaceuticals and Medical Devices Agency</p>

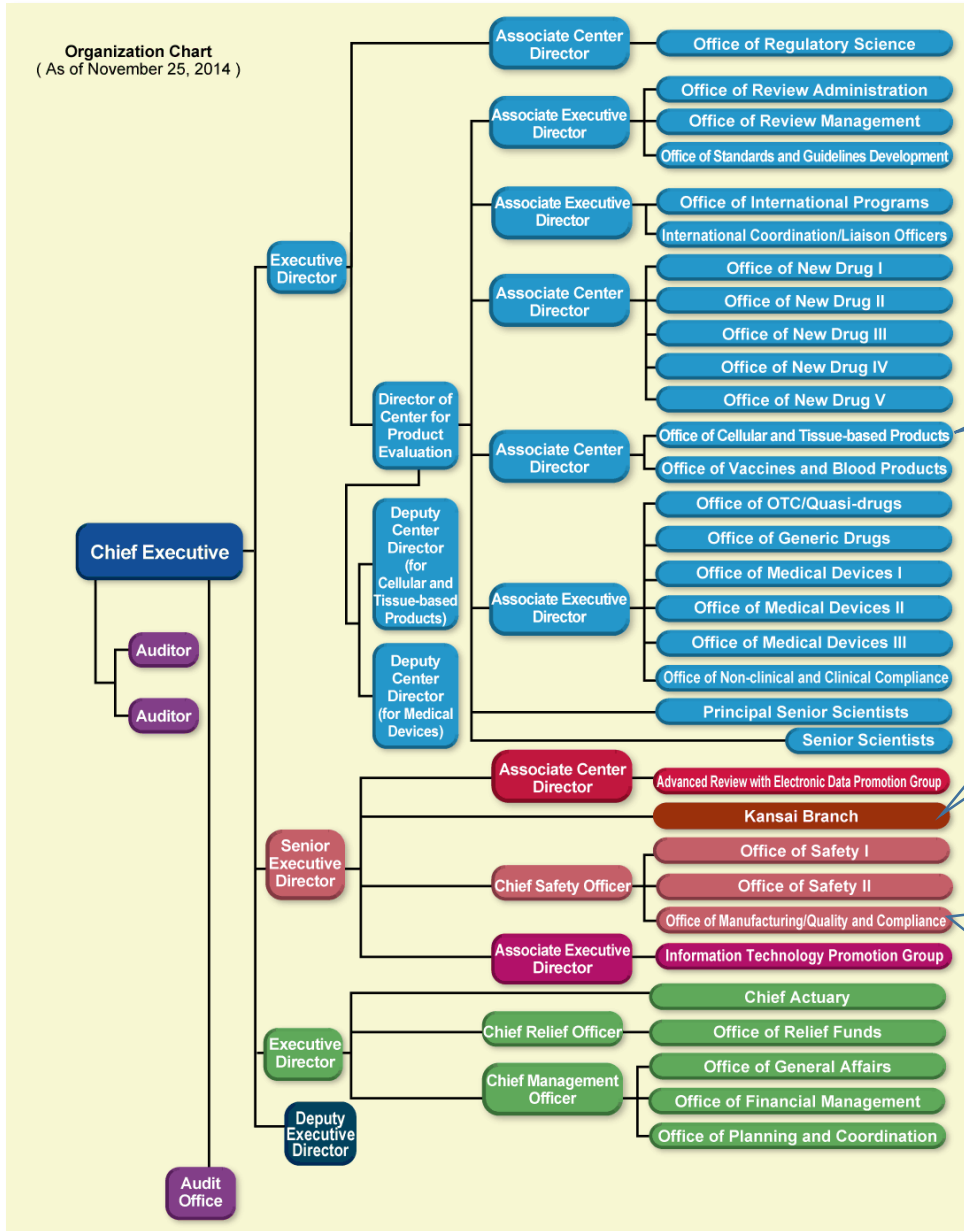
Activities of GMP inspectorate committee

1. Harmonize Quality systems
(Update of SOPs, Self inspection...)
1. Update GMP guidelines
2. Develop training programs for lead/senior inspectors
3. Share training tools (Mock inspection)
4. Share global information
5. Hold committee meetings 2-3 times/year
6. Discussions as necessary



- Improving risk-based inspection methods and skills
- Promoting global competitive inspectors

Organization chart of PMDA

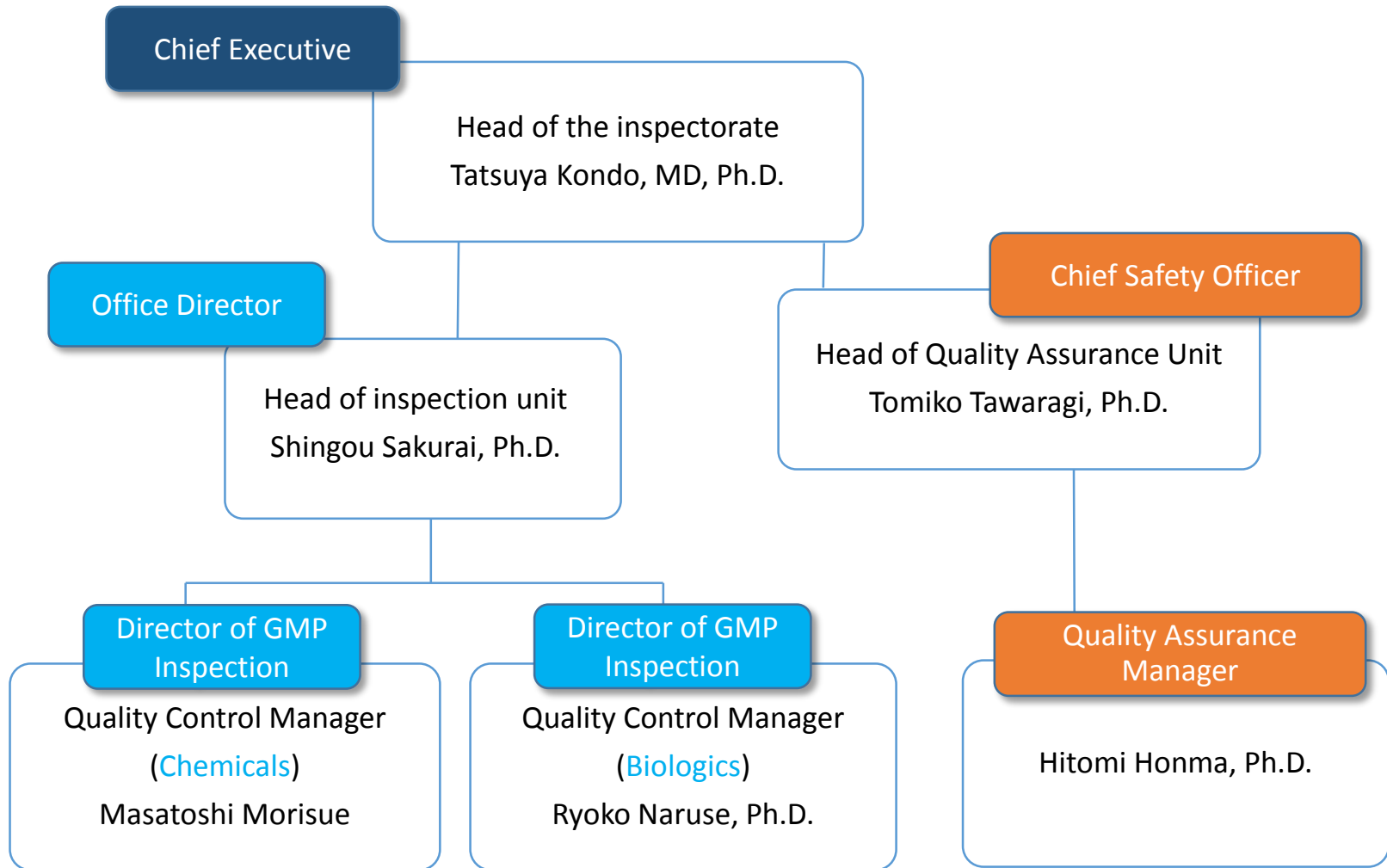


Office of Cellular and Tissue-based Products

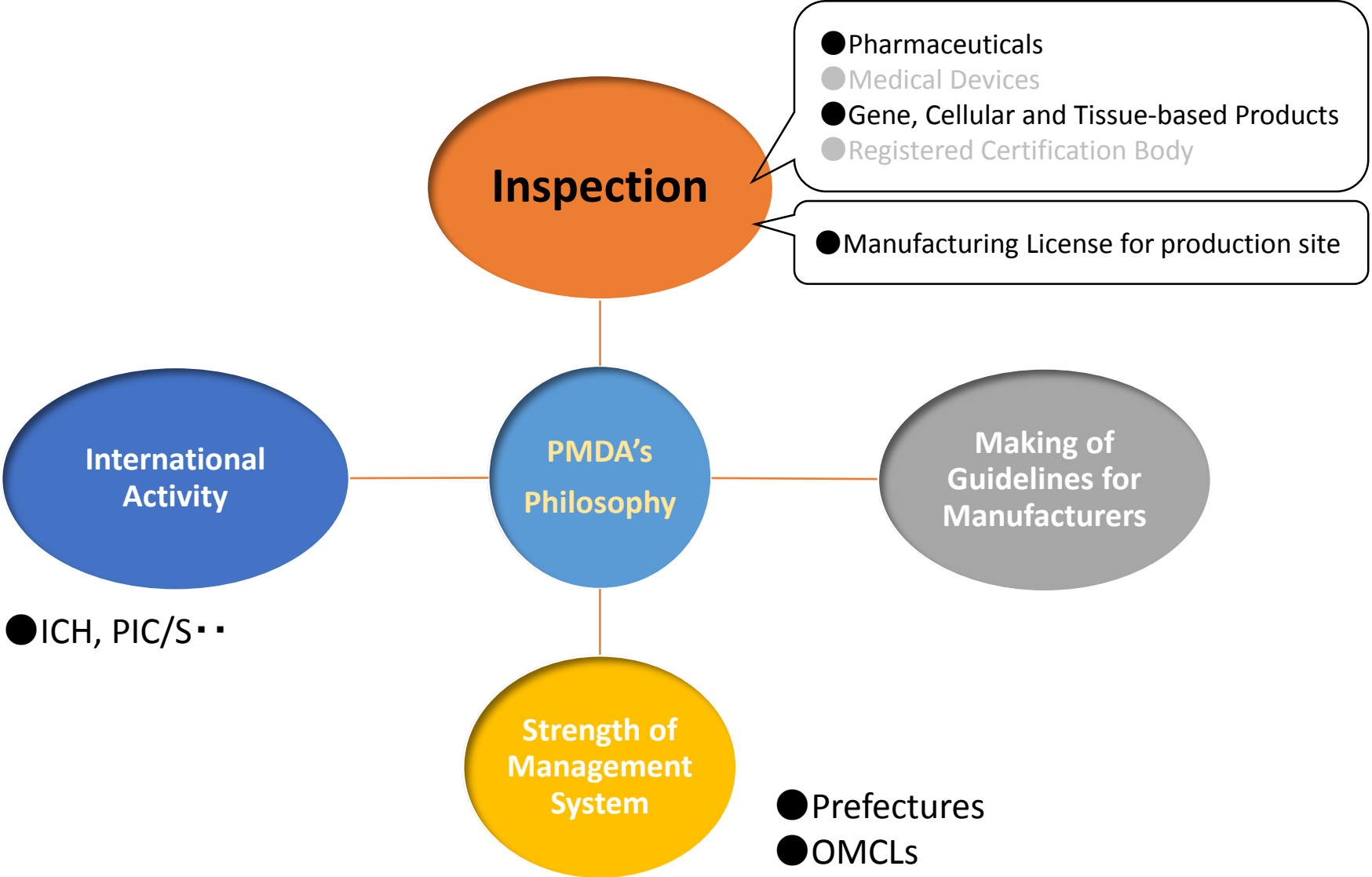
Inspection unit, Kansai Branch

Office of Manufacturing/Quality and Compliance

Key personnel in our Quality System



Our activities



Number of GMP inspectors in PMDA

Tokyo Head Office (On-site and Desktop inspection)

- 2 Directors (Biological/Chemical)
- 8 **Senior** Inspectors
- 5 **Lead** Inspectors
- 5 Inspectors

Kansai Branch (Osaka-city) (On-site inspection Only)

- 2 **Senior** Inspectors
- 2 Inspectors

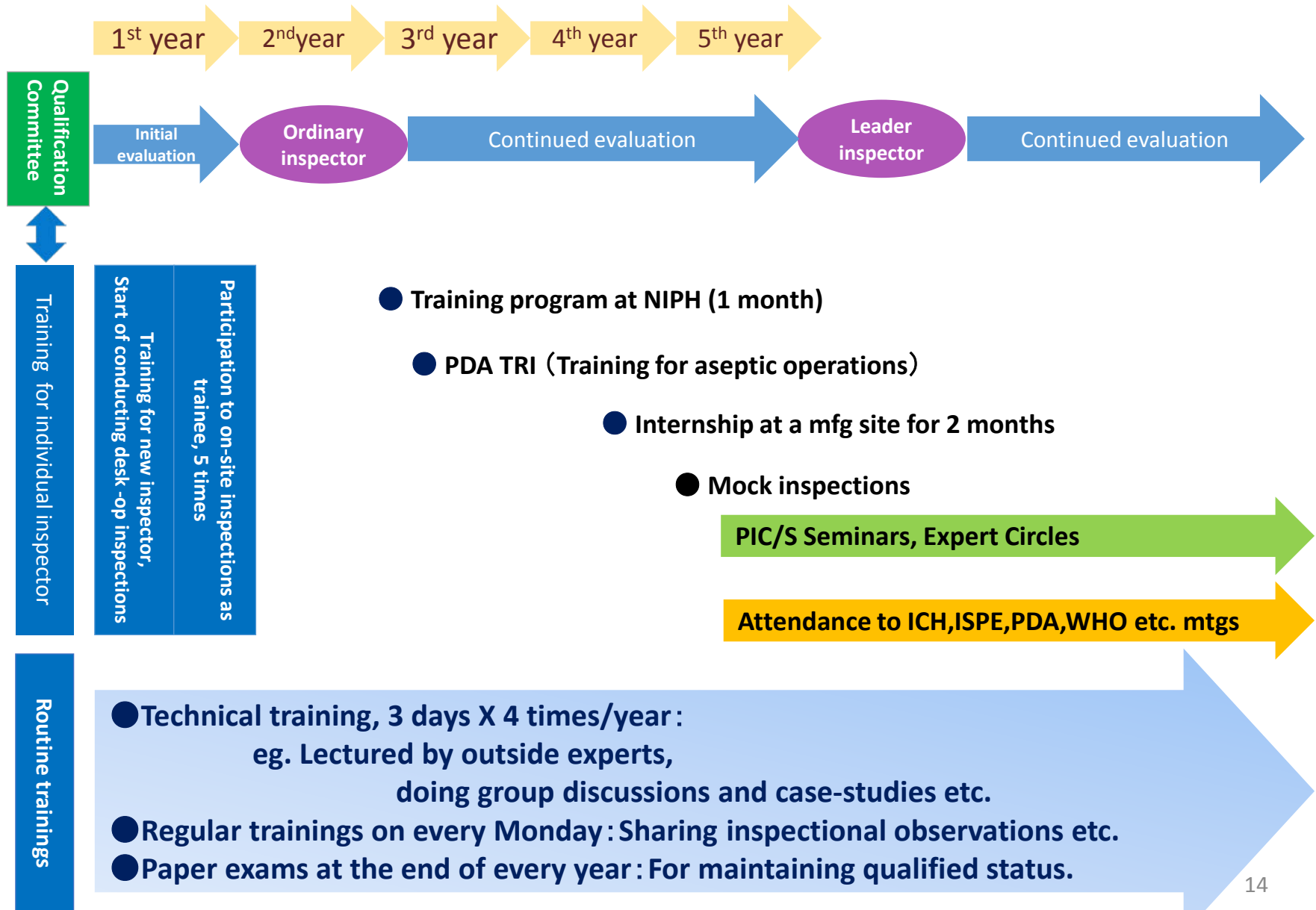
24 Inspectors

Performance of inspection

- **Total Number of Inspections conducted by PMDA
(Domestic and Overseas)**

	<u>Total</u>	<u>(on-site)</u>
• April 2011 - March 2012	1,283	(185)
• April 2012 - March 2013	1,593	(198)
• April 2013 - March 2014	1,415	(168)

Qualification of inspectors



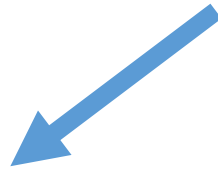
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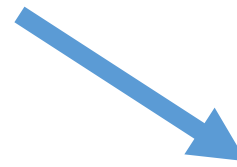
On-site or Desktop inspection



Selection of Inspection Method



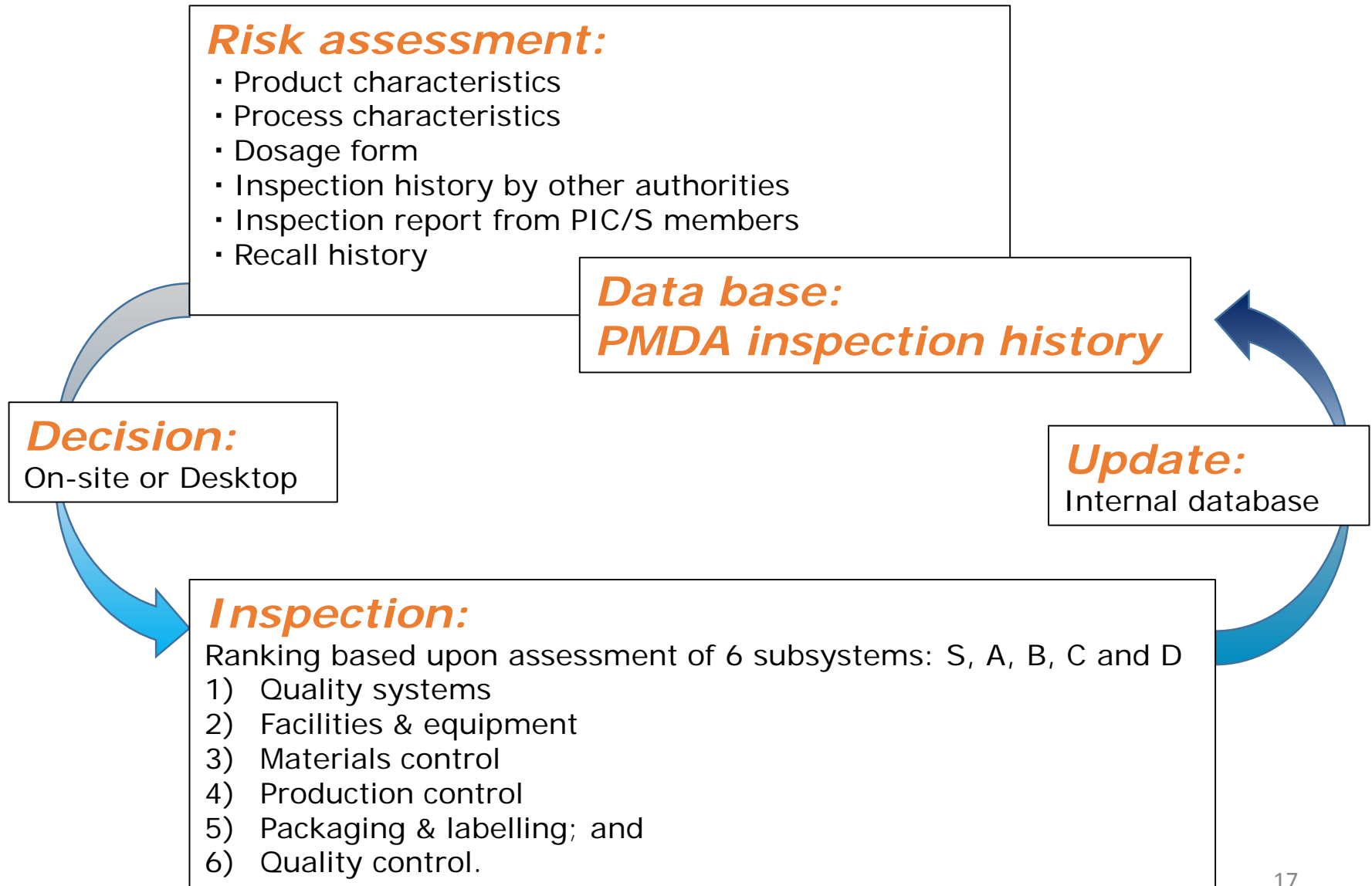
On-site inspection



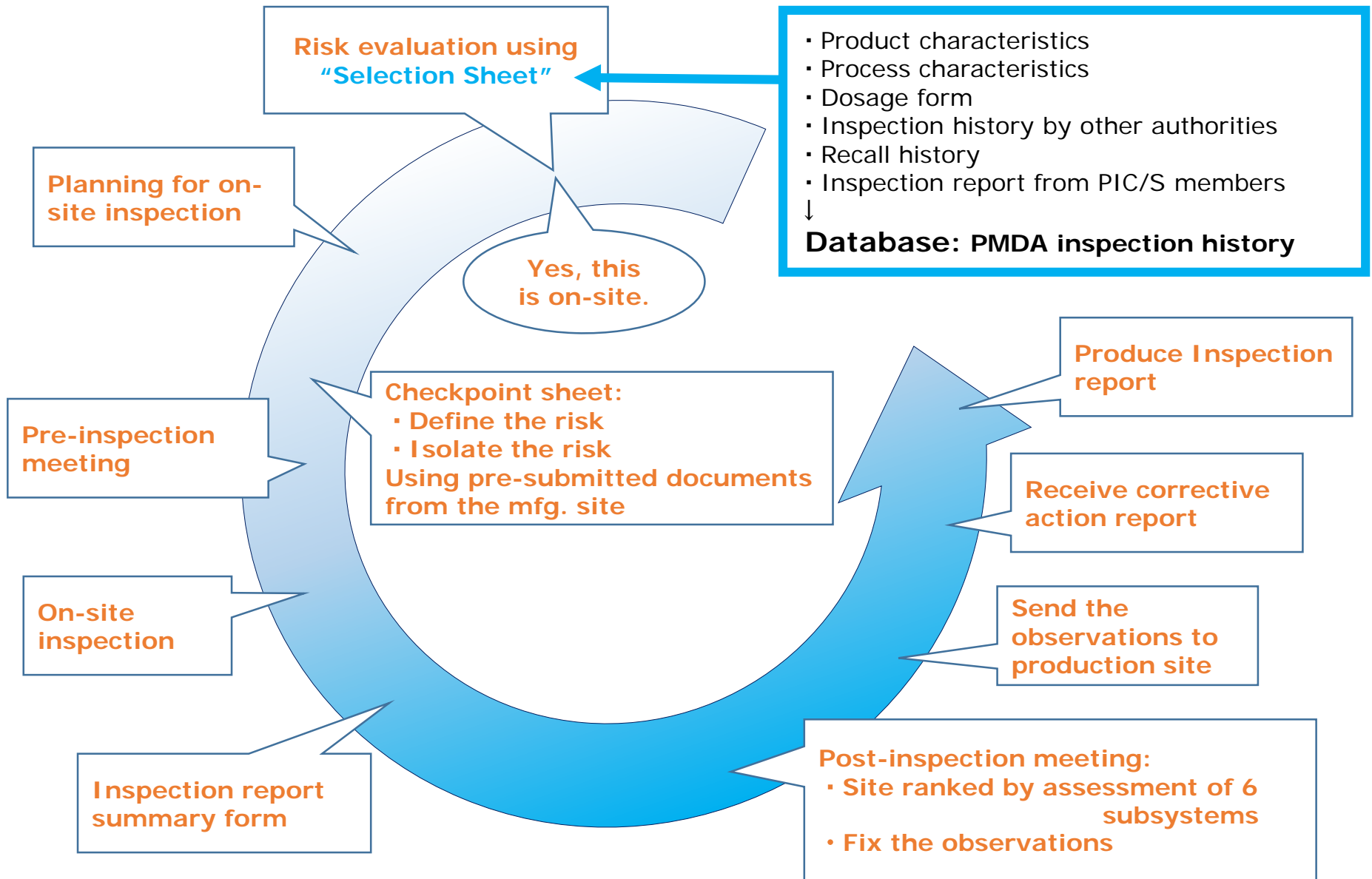
Desktop inspection

- ✓ Product
- ✓ Manufacturing Process
- ✓ Results of previous on-site inspections etc...

Risk-based decision making cycle



Events for on-site inspection



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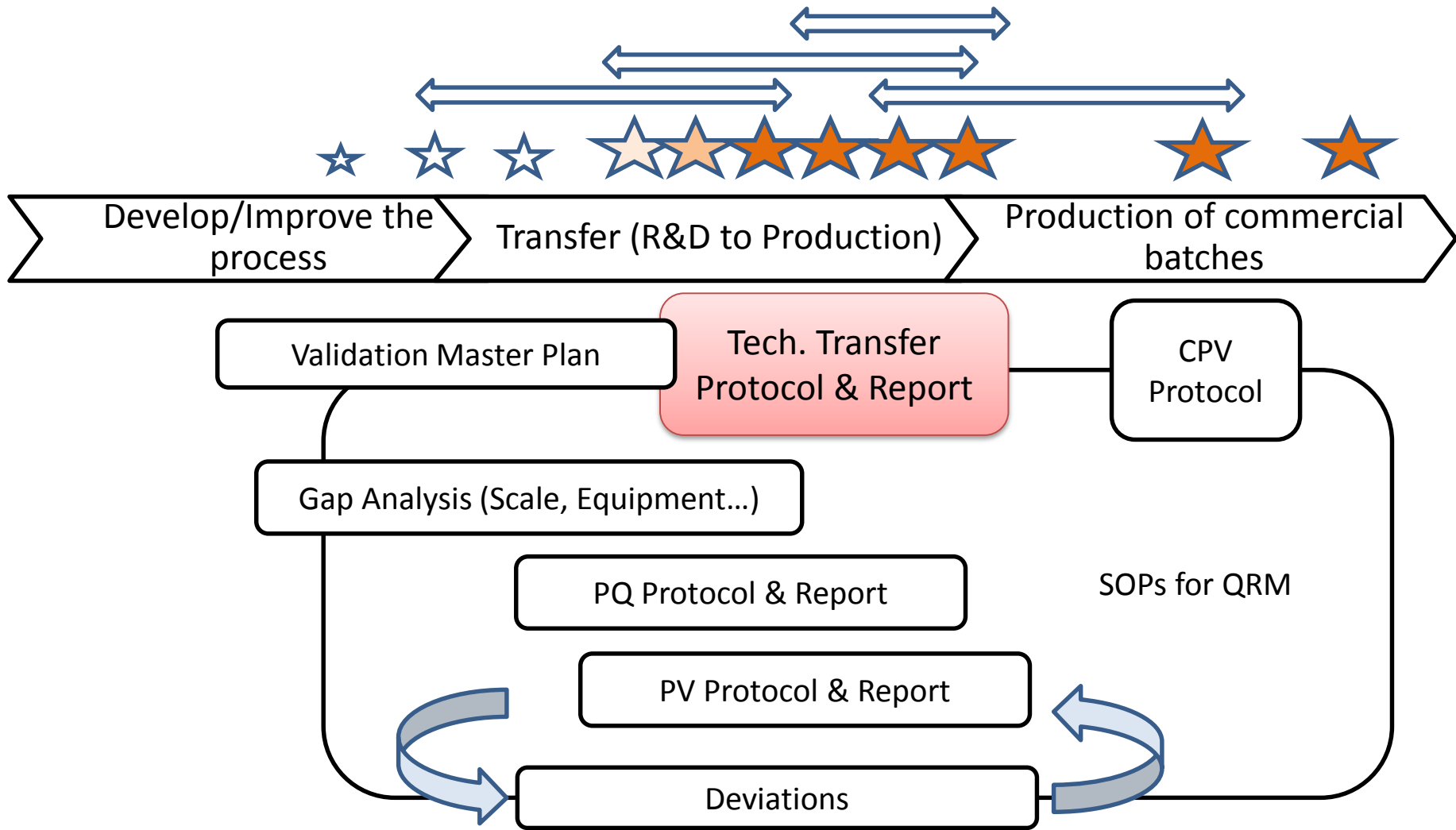
MHLW's policy :

The GMP inspectorates should enforce the GMP regulations on a risk basis in principle.

1. GMP requirements stipulated in the legislations should be enforced **according to the risk**.
2. Manufacturers are allowed to apply any manufacturing practices that are not explicitly stipulated in the legislations, however, **scientifically** sound to achieve equivalent or better **quality** and/or **risk** management than the methods defined in the legislations.

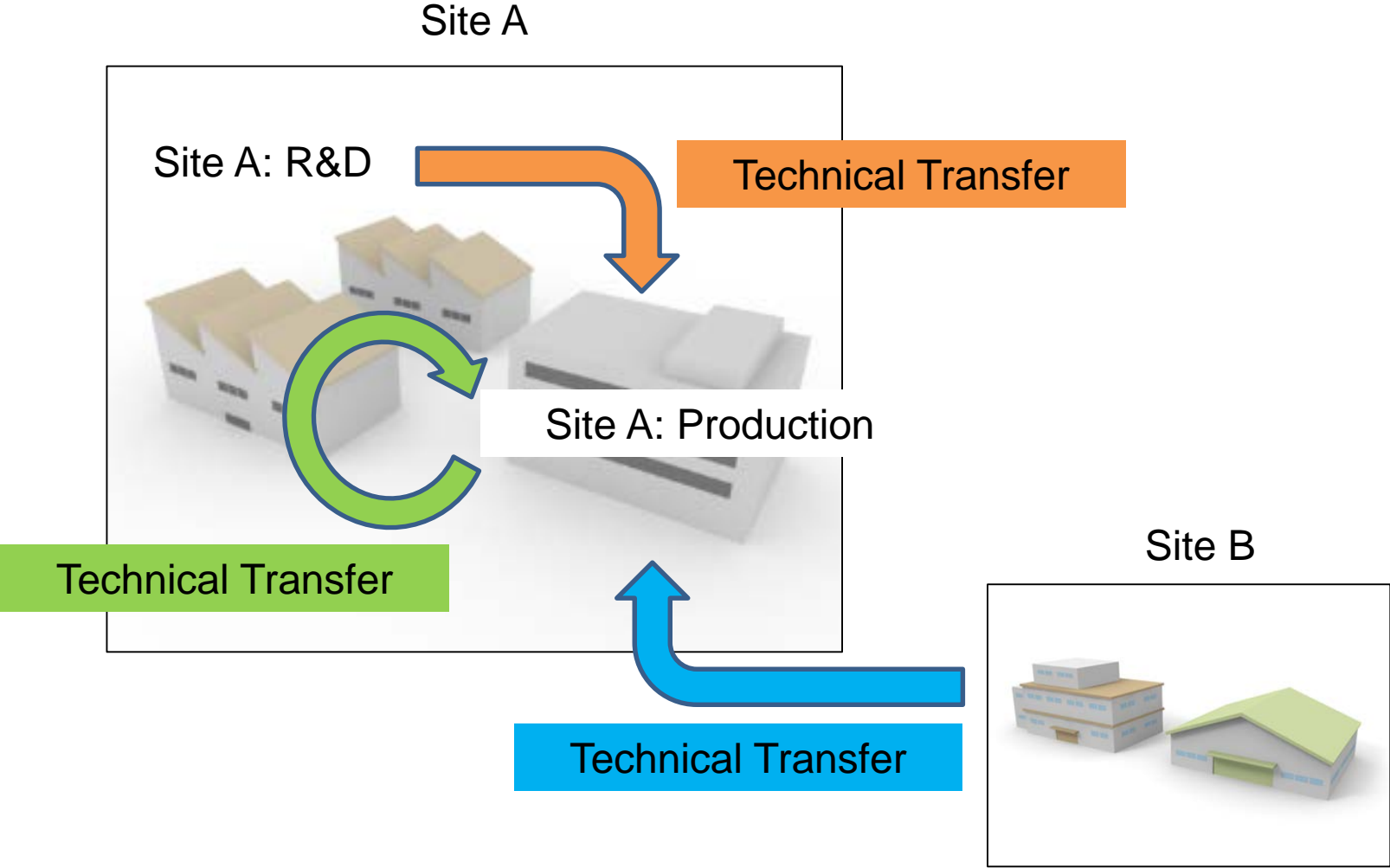
Reference: MHLW: [Viewpoints on application of PIC/S GMP Guide] (in Japanese).
Administrative Note, 1 Feb. 2012.

Case 1: Which documents should we check?



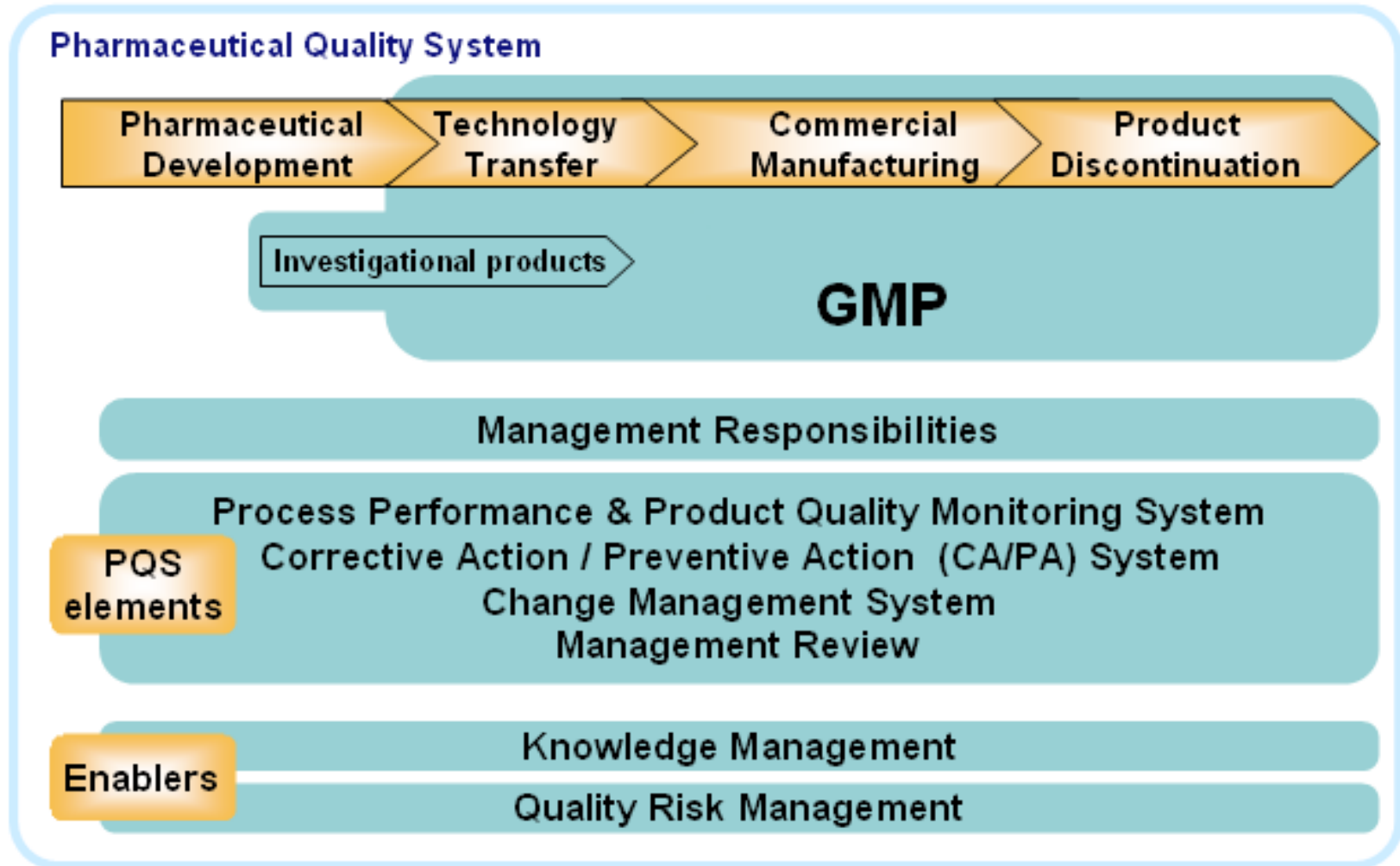
Inspectors should select documents based on risks.

Case 2: Which documents should we check?



Inspectors should select documents based on risks.

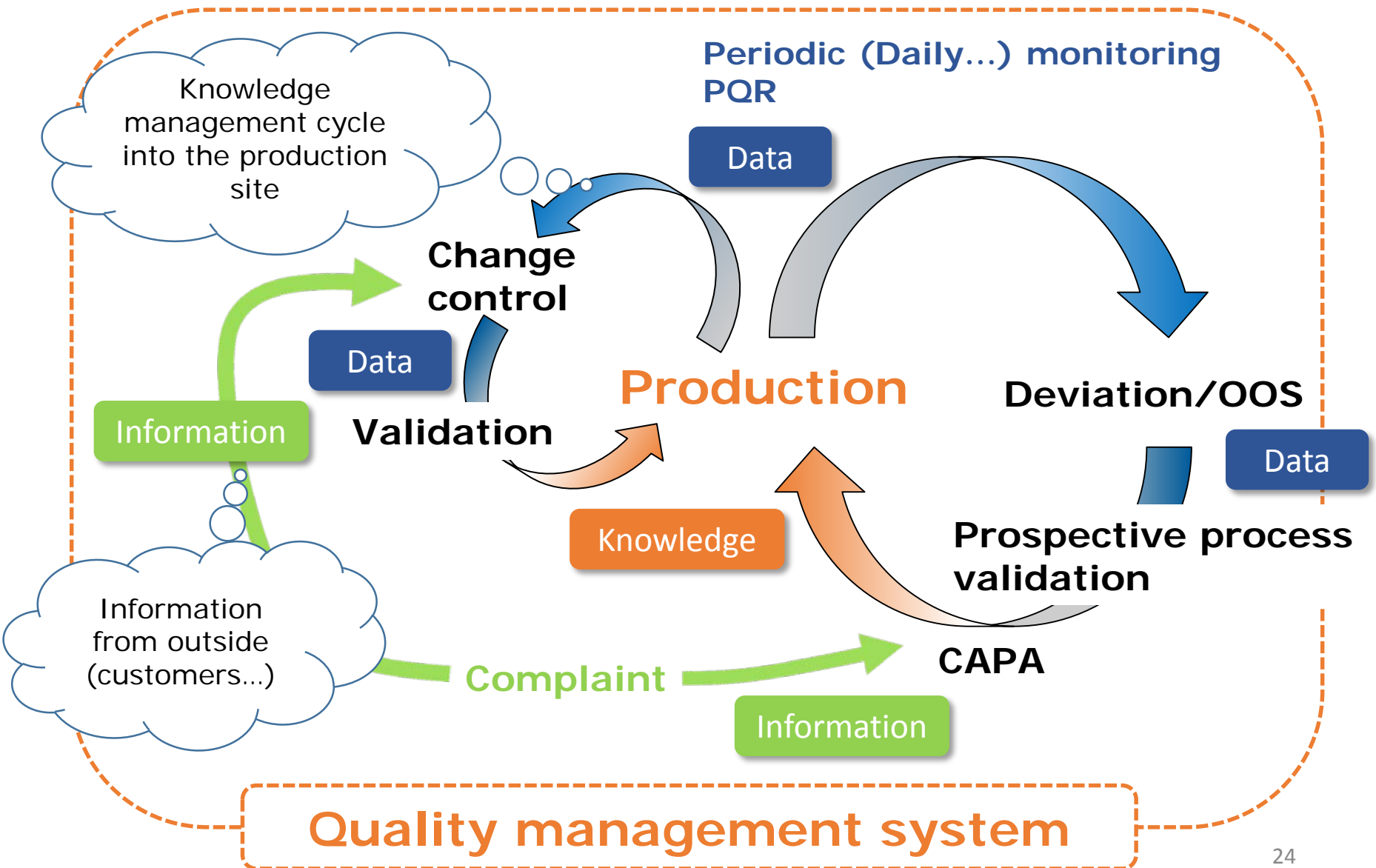
Pharmaceutical Quality System - ICHQ10



Reference: ICH Training Materials for Q8/Q9/Q10

<http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10/presentations.html>

Knowledge management cycle



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Guiding principles for drug recall in Japan (1)

Concept of decision making: Recall

1. **Efficacy and safety**: When the drug is of any concern about safety, shows insufficient efficacy, or is unjustifiable on safety, the drug should be recalled.
2. **Compliance**: When the drug is non-compliance with the approval conditions or other legislation requirements, the drug should be recalled.
3. **Foreign substances** (according to its type and dosage form of the drug):
The type of foreign substances: i.e. intrinsic substances(e.g. glass fibers); extrinsic substances (e.g. wood chips); or biological substances (e.g. hair, worm etc.) should be considered. When any aseptic drug is contaminated with extrinsic or biological foreign substances, the drug should be recalled. In case any non-aseptic drug is contaminated with biological foreign substances, the drug should be recalled.

Reference. MHLW: [Recall of drugs, medical devices etc.] (in Japanese). *Iyakuhatu* No.237, 8 Mar. 2000, amended by *Yakushokuhatsu* No.0730008 in 2003, No.0528004 in 2004, No.0331021 in 2005 and No.0322-3 in 2011.

Guiding principles for drug recall in Japan (2)

Concept of decision making: Recall

1. Unless all the following conditions are met, the quality defects should be regarded as affecting all lots.

A: The cause of the quality defects and relevant processes are identified.

B: Appropriate actions have been taken to prevent recurrence of the quality defects and no problem is detected on the GMP.

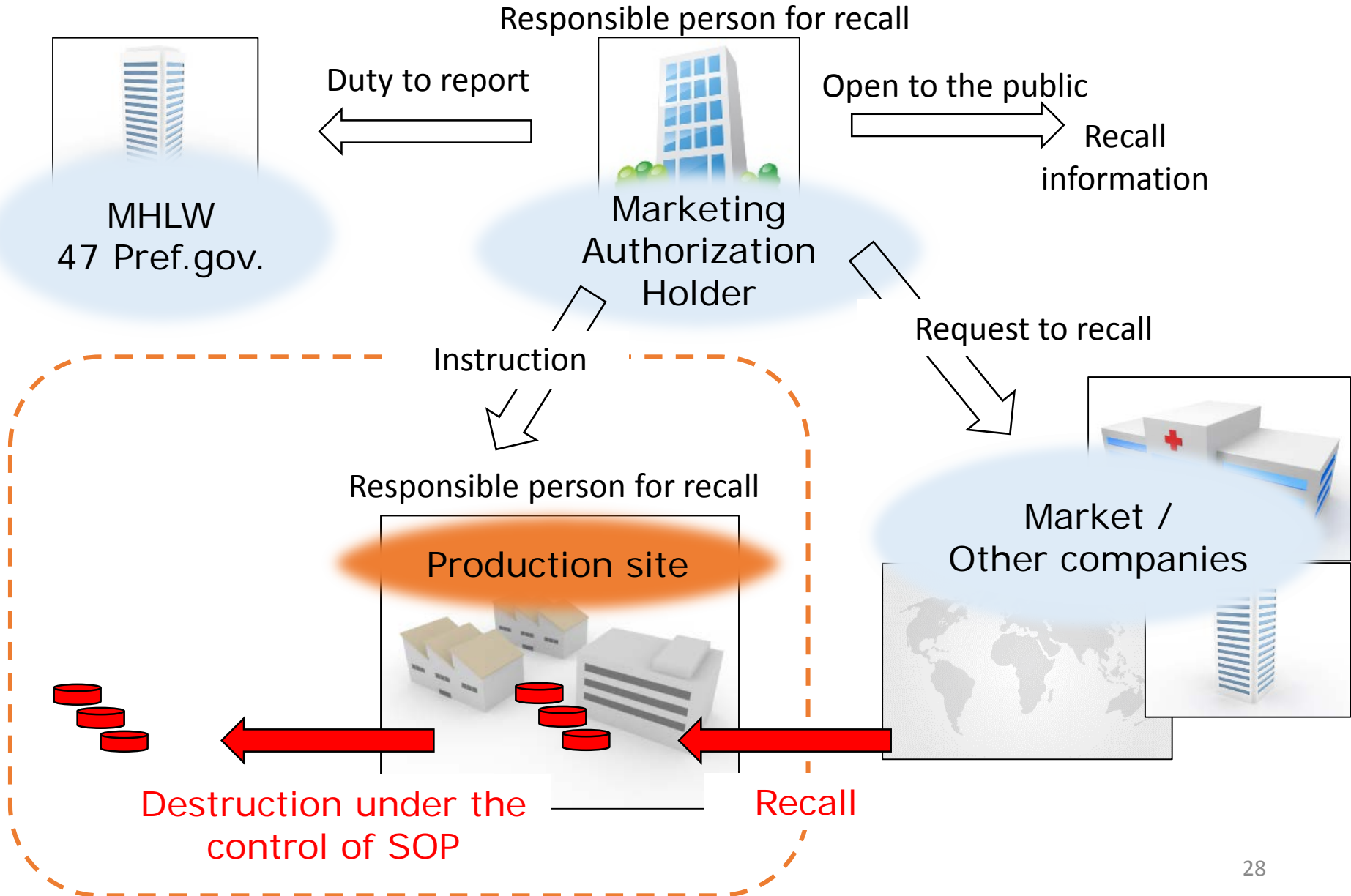
C: There are no abnormalities in quality of the retention samples.

D: No problem is detected on the GQP that affects product quality.

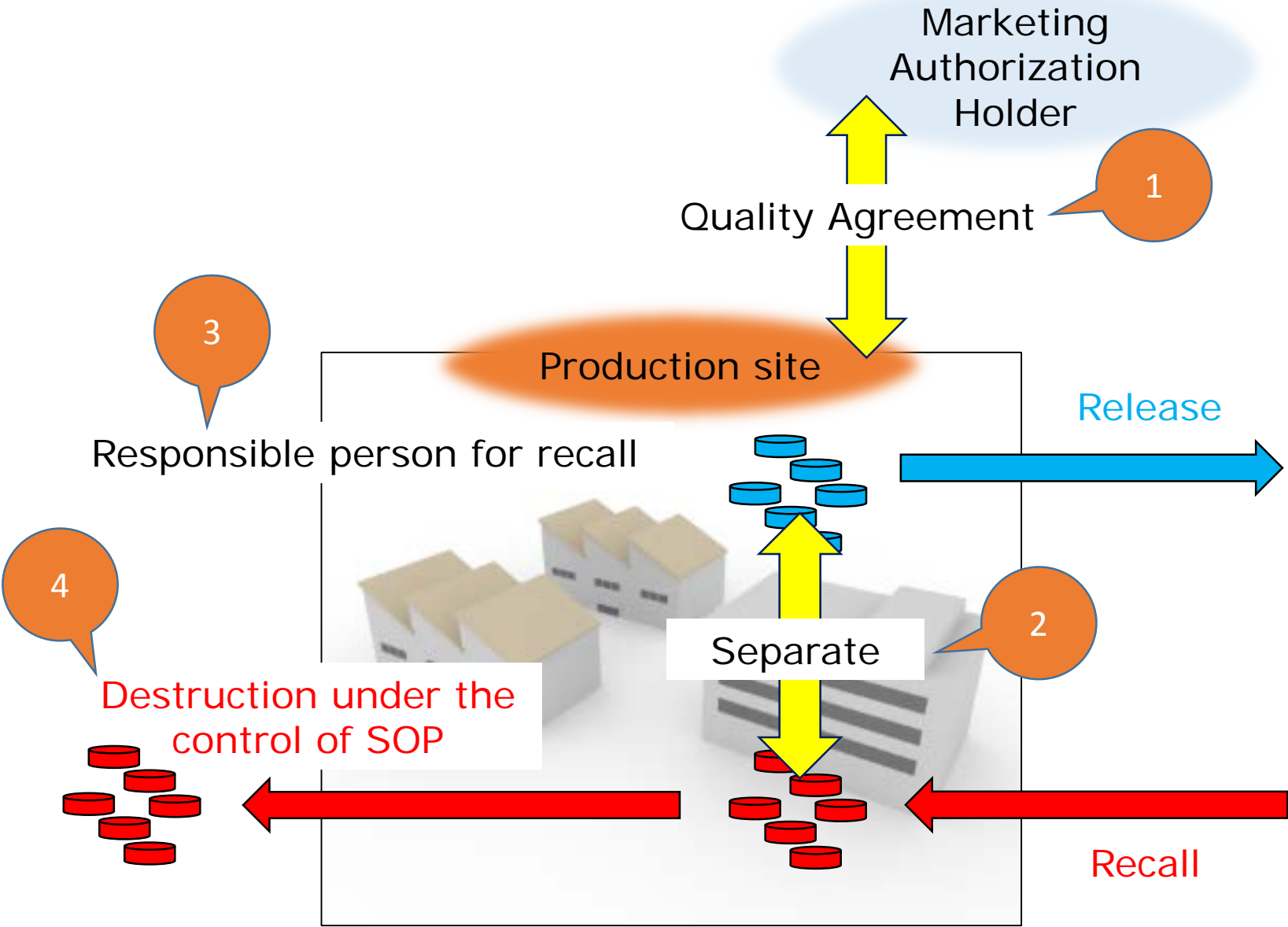
2. Even though it has been once determined the quality defects do not affect all lots, however, the defects have been indeed detected in two or more settings, the drug should be recalled in light of incidence of the defects.

Reference. PFSB-DG, MHLW: [Recall of drugs, medical devices etc.] (in Japanese). *Iyakuhatu* No.237, 8 Mar. 2000, amended by *Yakushokuhatsu* No.0730008 in 2003, No.0528004 in 2004, No.0331021 in 2005 and No.0322-3 in 2011.

Recall



Check point in GMP inspection



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Future issues

1. Development of cooperation scheme among stakeholders (mutual benefit)
2. Understanding of different GMP regulations in each country
3. Training of Inspectors (Holding PIC/S Expert Circle Meeting, Continuous participation in PIC/S Expert Circle Meeting, Seminar, revision working team of PIC/S Guidances, IWG(Inspection Working Group) at EMA)
4. PIC/S accession will be effective for exchanges of information between authorities
5. Expansion of MRA scope between Japan and EU
6. ICH, other activities

Thank you for your attention.

