Examples of Observations in GMP Compliance Inspections, and Related Problems

(Manufacturer/Market Authorization Holder/In-country Caretaker of MF, Etc.)

Office of GMP/QMS inspection,
Pharmaceuticals and Medical Devices Agency

CPhI Japan 2013
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Tokyo Big Sight

* The slides in Japanese are the official edition.

Today's agenda

1. Introduction (the main topic for today)
2. Overview of GMP on-site inspections by the PMDA
3. Cases of non-compliance in recent GMP compliance inspections
4. Examples of observations in GMP on-site inspections
5. Problems in GMP control
   (Marketing authorization holder/In-country caretaker of MF)
6. Conclusions

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1. Introduction (the main topic for today)

— High-quality drug products for patients —
(Safe products and stable supply)

- Marketing authorization holders, manufacturers (manufacturing sites) and representatives of manufacturers (trading companies, representatives making applications for accreditation of foreign manufacturers, in-country caretakers of MF, etc.), regulatory authorities
  - Appropriate GMP control (GQP control)
  - Smooth GMP compliance inspections
    Both inspectors and inspectees want reasonable inspections.

What is needed for reasonable inspections → Close collaboration and communication between a marketing authorization holder and the in-country caretakers of MF/manufacturers, understanding of Japanese pharmaceutical regulations and improved knowledge

★ **Non-compliance cases/examples of observations in recent GMP compliance inspections.**
★ **Responsibilities of manufacturers, marketing authorization holders, and in-country caretakers of MF.**

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2. Overview of GMP on-site inspections by the PMDA

Inspections conducted by the PMDA

Inspection of facilities and equipments

- **Licenses for domestic facilities (for biological products etc.) that require a license by the Minister**
- **Accreditation of foreign manufacturers**

GMP compliance inspection

- **New drugs**
- **Biological products etc.**
- **Drug products manufactured at foreign manufacturing sites**

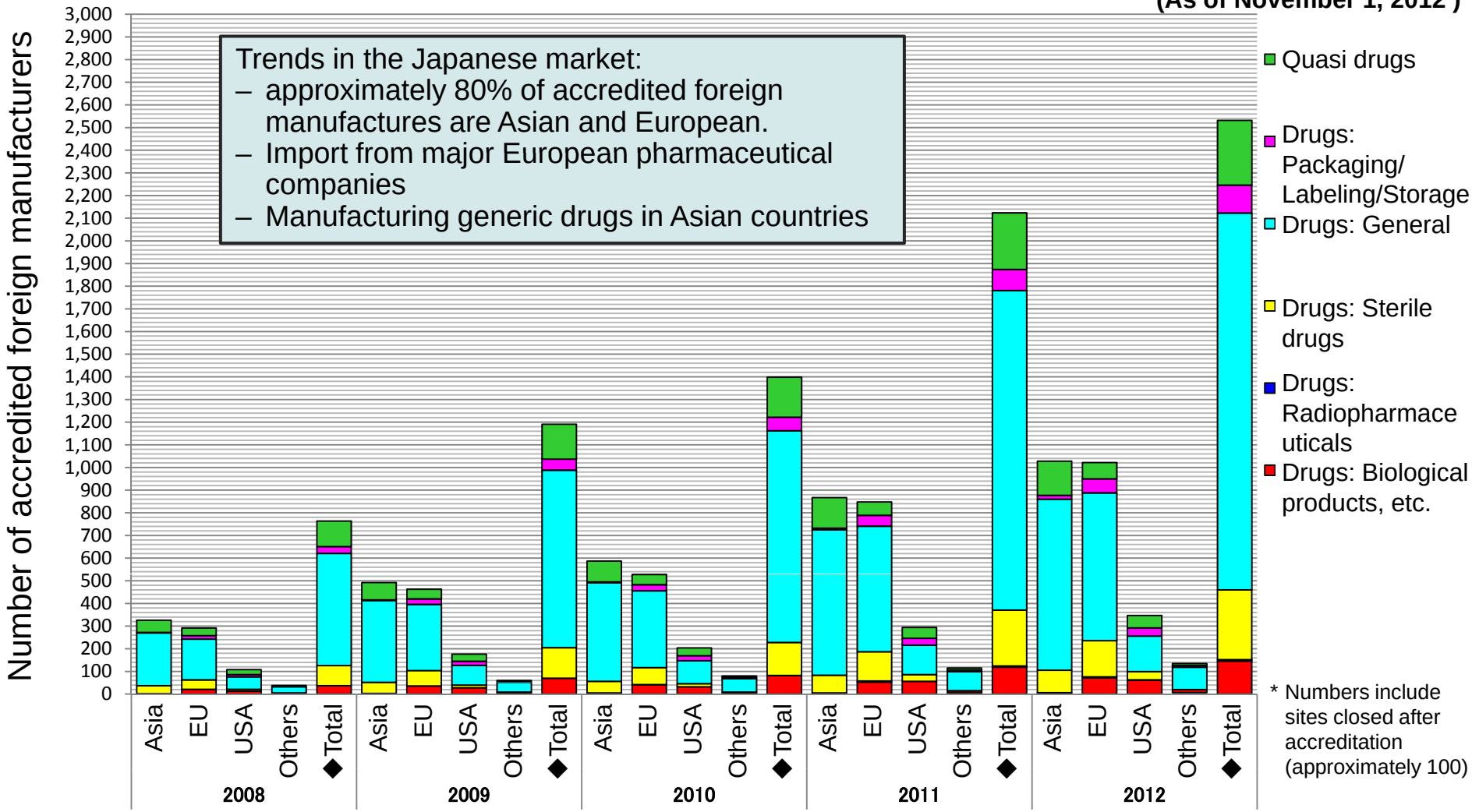
Trends in the Japanese market

- **Of accredited foreign manufacturers: approximately 80% are Asian and European.**
- **Import from major European pharmaceutical companies**
- **Manufacturing generic drugs in Asian countries**

2. Overview of GMP on-site inspections by the PMDA

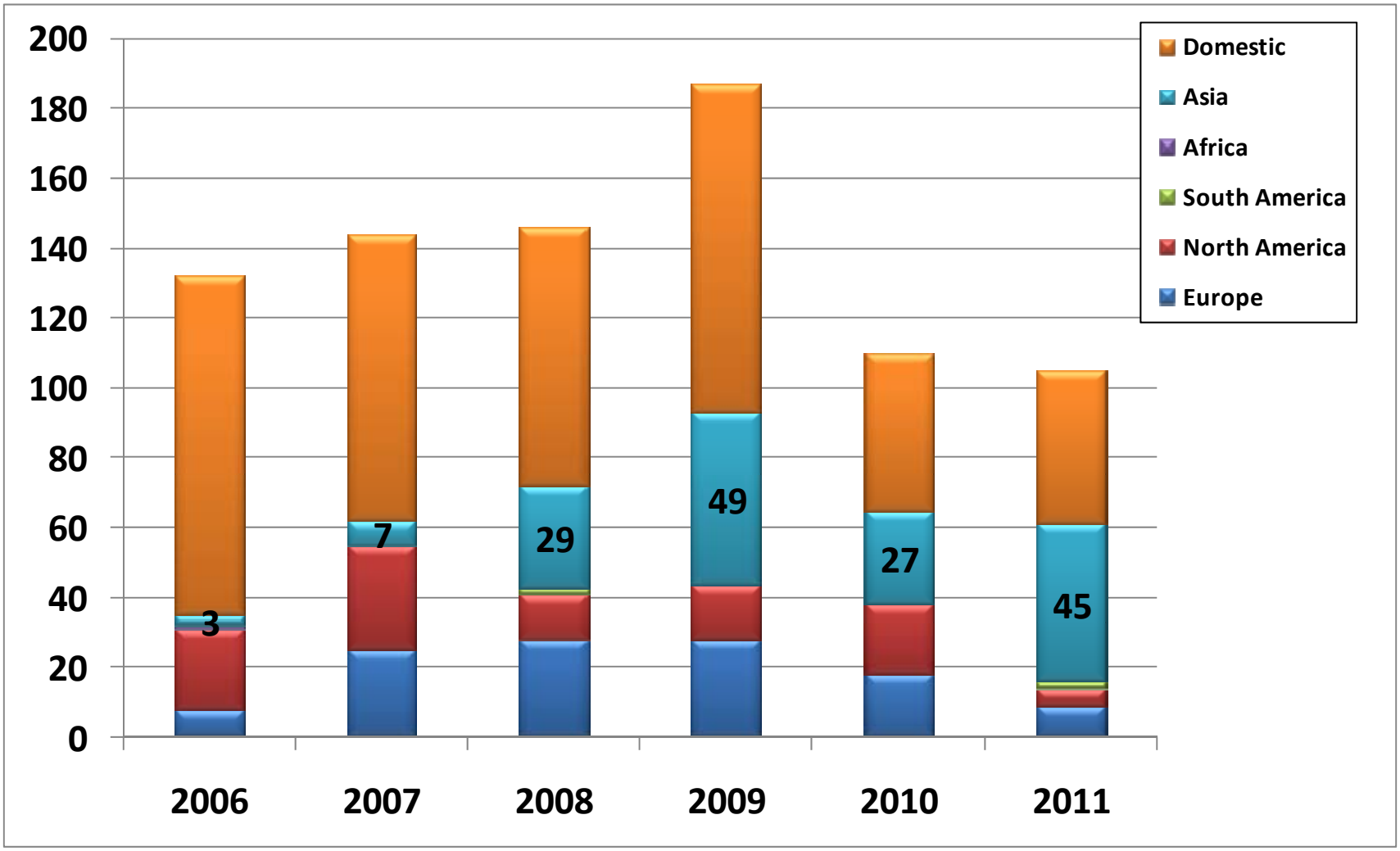
[Accreditation of foreign manufacturers: Totals by fiscal year and area] Fiscal 2008 – 2012

(As of November 1, 2012)



2. Overview of GMP on-site inspections by the PMDA

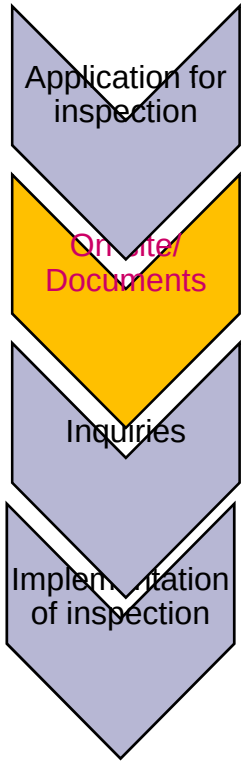
[Number of domestic and foreign on-site inspections: Annual changes by area] (April 2006 – March 2012)



2. Overview of GMP on-site inspections by the PMDA

Procedure for determining on-site inspection

From application for inspection to commencing inspection



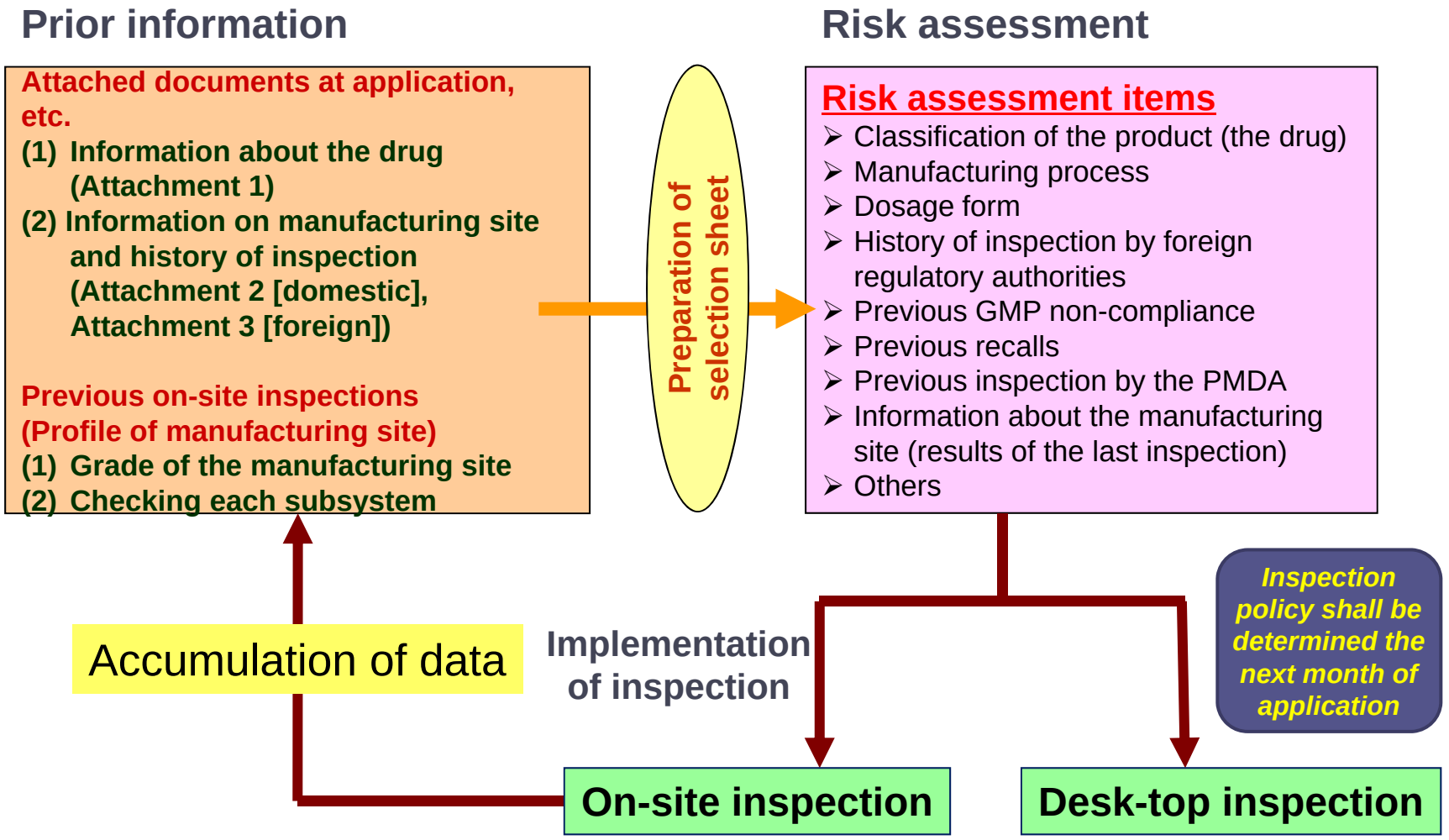
- **Outlines of product(s) subject to inspection: Form 1**
- **Outlines of drug manufacturing site (foreign manufacturing site): Form 3**

- **Risk assessment**
- **Determination of inspection method**

- **On-site inspection: Arrangement of schedule**
  → Documents submitted in advance
- **Desk-top inspection: Documents for inspection by the PMDA**

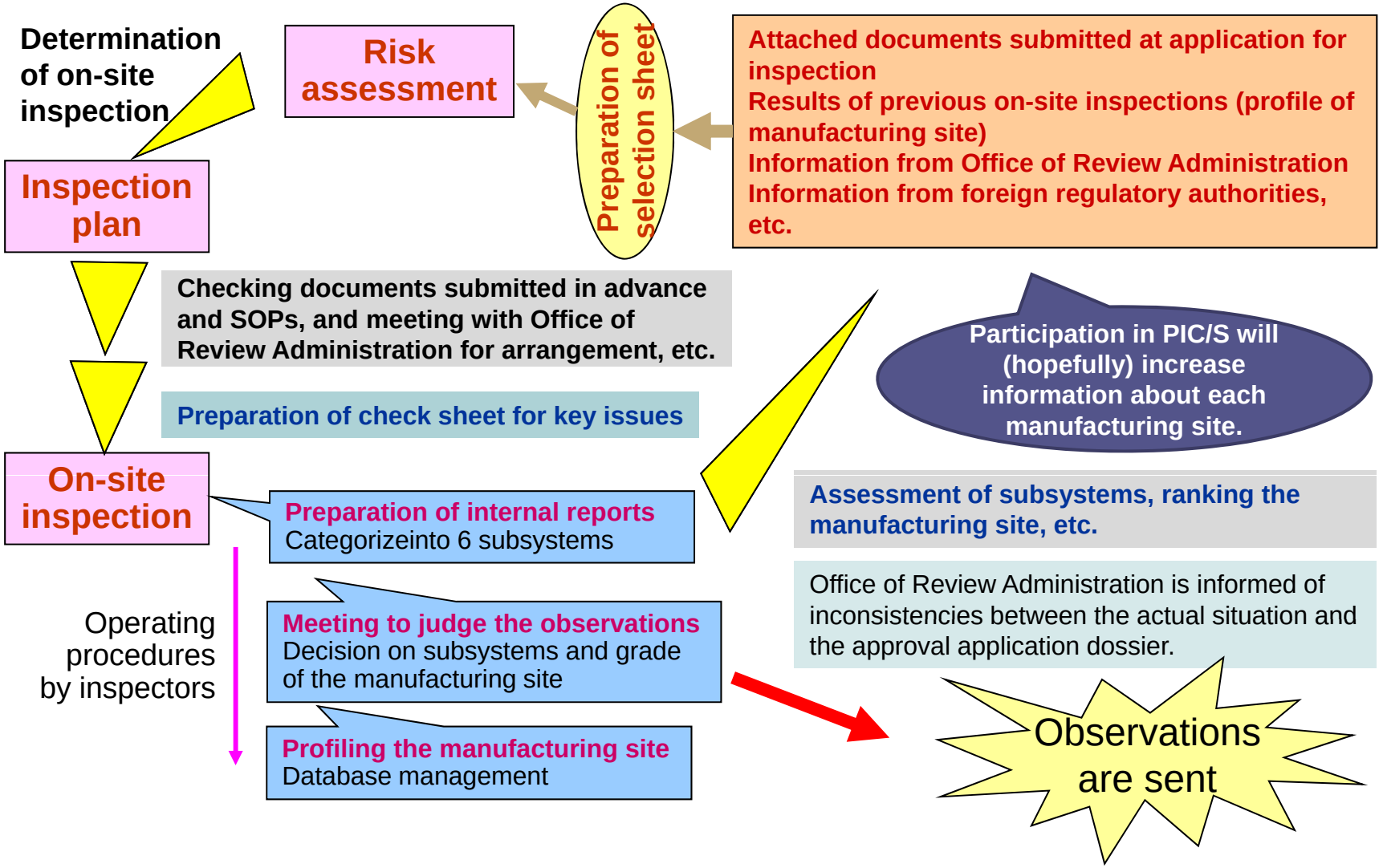
- **On-site inspection: Issues observations by the PMDA, grading the manufacturing site**
- **Desktop inspection: Checking with inquiry-based documents**
- **Presence or absence of inconsistencies**

Selection of inspection sites according to risks



Note: For attached documents, see Notification dated October 27, 2010.

Decision-making cycle for inspection policy



2. Overview of on-site inspections by the PMDA

PMDA internal assessment data: Ranking manufacturing sites

Based on-site inspection results (assessment), manufacturing sites are graded as S, A, B, C, and D (Degrees and numbers of defects, and assessment by subsystem are totaled for the final grading).
D : Manufacturers in non-compliance with GMP
C: Manufacturers in compliance with GMP but need to be given continuous instructions

Main area	Number of on-site inspections Dec. 2007–Oct. 2012	Grade of manufacturing site		Total	% of C and D
		C	D		
Asia (excluding Japan)	181	50(12)	5(3)	55	**30%**
EU	102	4(2)	0	4	4%
North America	66	5(1)	1(1)	6	9%
Central and South America	13	2(1)	0	2	15%
Japan	348	58(19)	5(5*)	63	18%

- The proportion of sites rated C and D remain high in Asia (excluding Japan).
- D in inspections for renewal (periodic inspections) are problematic.

Grade S, A, B and C are all “in compliance”.

Numbers in parentheses indicate inspections for renewal, and asterisks indicate on-the-spot inspection.

Reinforcement of monitoring

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3. Cases of non-compliance in recent GMP compliance inspections

Non-compliance case (No.1)

1. Inspection target
   The inspection was carried out on a foreign sterile product manufacturing site (freeze-dried preparations), and it was a periodic inspection.

2. Articles violated: Article 23 Section 1 and Article 24 Section 1 of the Ministerial ordinance
   Lack of sterility assurance due to defects in manufacturing conditions in the aseptic area (grade A)
   (1) After sterilization, vials and rubber stoppers were stored insufficiently protected in a grade B area, and were brought to a grade A area and used. All freeze-dried preparations were capped but there was no proper confirmation of whether they were well sealed, so they were insufficiently protected, and transported through a corridor in a grade B area to the clamping room.
   (2) Workers could freely enter the area, which was required to be grade A, at anytime (frequently during manufacturing) to carry out sterile filling operations and carry vials to freeze dryers, etc.
   (3) In the above formulation process, products were being produced without one-way air flow in the grade A area. The defect was known but was not improved.

* *Serious defects other than* with *the sterile product were not noted in the manufacturing control. However, in terms of the quality system (management/control system)* for *the manufacturing site* as a whole*, the defect may have some impact on the manufacturing control* of *other than the sterile product.*

3. Cases of non-compliance in recent GMP compliance inspections

Non-compliance case (No.2)

1. Inspection target
   The inspection was carried out on a foreign manufacturing site (API), and it was a periodic inspection.

2. Articles violated
   Article 6, Article 10 Section 1 items 3 and 5, Article 11 Section 1 items 1 and 2, Article 14 Section 1 items 1 and 2, Article 15, Article 16 Section 1 items 2 and 3, and Article 19 Section 1 item 3 of the Ministerial ordinance
   Most of the records required have not been kept.
   (1) Management/control systems were not implemented.
   There were SOPs for deviation control, complaint handling (quality information management). However, there were no records of them.
   The workers did not understand what a “deviation” is (lack of capabilities and training).
   (2) Reliability of the test data could not be ensured.
   Only test results were kept, and there was no evidence of the test records kept.
   Therefore, it was not certain whether the tests were actually carried out.
   (3) There were no records of actual production quantities.
   Data on the yield and yield rate were missing. How surpluses were handled was not traceable.

3. Cases of non-compliance in recent GMP compliance inspections

Non-compliance case (No.3)

1. Inspection target
   The inspection was carried out on a domestic manufacturing site (biological products), and it was a for-cause inspection.

2. Articles violated
   Article 6 Section 1, Article 10 Section 1 item 9, Article 12 Section 1, and Article 15 Section 1 item 1 of the Ministerial ordinance
   (1) Packaging activities including opening and resealing were routinely conducted when deviations occurred in the products released at the manufacturing site. These deviations were recorded in an “operation memorandum”, not in any GMP documents; no records were kept in the GMP manufacturing documents.
   (2) The above deviations were not known by the quality unit, and the products were distributed without reassessment for release.
   (3) The above handling was conducted under the direction of a manager. The necessity of documenting these deviations in the GMP documents was not understood by the person in charge.

3. Cases of non-compliance in recent GMP compliance reviews

Non-compliance case (No.4)

1. Inspection target
   The inspection was carried out on a foreign manufacturing site (sterile API), and it was a periodic inspection.
   → There were products formulated (filled) and released to the market without sterilization process in Japan.

2. Articles violated
   Article 23 Section 1 item 1 and Article 24 Section 1 items 1, 3 and 7 (a) of the Ministerial ordinance
   There was a lack of sterility assurances with respect to both the facility and operation. The risk of microbial contamination was very high.
   (1) Handling of primary containers after sterilization
   The sterilized containers were handled under class 10,000 conditions, and the conditions were improved. However, the installed clean booth could not be qualified.
   (2) Defects in the condition of charging raw material, which should be charged under the aseptic conditions
   The charging operation was performed under class 10,000 conditions, and it should have been done in an aseptic area. A clean booth was installed to improve the situation. However, the design was not appropriate for ensuring aseptic conditions.
   (3) Aseptic handling was not conducted by workers engaged in a series of operations.
   ⇒ They were not appropriately trained to conduct the aseptic processing.

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Quality system

- There were no written procedures for change control, deviation control, and document control.
  (They were being prepared.)

- The process of checking for the presence or absence of deviations and the details thereof was not incorporated in the product release procedure.

Change control

- Defects in evaluating changes
  - There were no records of who decided the importance of changes and how it was decided.
  - The quality unit only checked the contents of the plan when approving an implemented change; it did not assess the influence on quality and various assessment results.
  - There were no written procedures for the quality unit to check the appropriateness of the change results.

- Cases not conforming to the change control procedure
  - The in-process control test items were implemented only by changing the SOPs.
  - A change of widening the tolerance of the intermediate product specifications was implemented without documenting it.

Facilities and equipment management

- There was no plan or record of calibration and maintenance.
- Defects in management of water for production (defects in management to prevent microbial contamination)
  - The purified water pipework was unidirectional; purified water was stagnating in the pipework except when it was used once a month. It was not sterilized periodically. Microbiological evaluation was not performed at the point of use.
- The reactor was rusty, and it was possible that contamination could occur.

Cleaning validation

- In the reactor cleaning validation, the results with the swab method were recorded as below the detection limit. However, the method (swabbed site, area, and method) was not specified. The detection limit was determined through a visual inspection of the used cotton-swabs.

- There was no cleaning validation of a shared chamber dryer.

Laboratory control

- **Unreliable test data due to defects in test records**

  (1) **Information showing that tests were performed under appropriate conditions was not documented.**
  For titration tests, only the numerical values of the results were recorded. Data on titers, titration reagent factors, reagent lots, or the results calculation process were not recorded. (The reagent preparation was not recorded, and raw data were not kept.)

  (2) **Issuance of the test record form was not controlled. (Data falsification and retesting were suspected.)**
  The test record form was issued by QA. There were no restrictions on issuance. There were a large number of test record forms discarded in a trash box in the laboratory.

Laboratory control

- **Defects in in-process control test procedures**
  - System suitability was not specified.
  - Column change conditions were not specified.
  - Column use history was not recorded.
  - Mobile phase preparation was not recorded.

Manufacturing control

- Manufacturing instructions were not documented. (They were given orally.)

- Defects in manufacturing instructions and records
  - Raw material lots were not recorded.
  - The weighing record did not include the name of the material weighed.

- In lot mixing, the test items before mixing were not sufficient.

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5. Problems in GMP control
(Marketing authorization holder/in-country caretaker of MF)

The number of manufacturing sites that the PMDA inspects

As of March 2012

- Foreign manufacturing sites

  Foreign manufacturing sites: Approximately 2,700

  - Accredited sites: 2385
    Asia (excluding Japan) and the Middle East: 941 (drugs: 801, quasi drugs: 140)
    Europe: 983 (drugs: 914, quasi drugs: 69)
    North America, Central and South America, Africa, Oceania: 461 (drugs: 398, quasi drugs: 63)
  - Manufacturing sites where accreditation is not required (API intermediates, APIs made from food products or other industrial products, etc.): Approximately 300 (approximate figure)

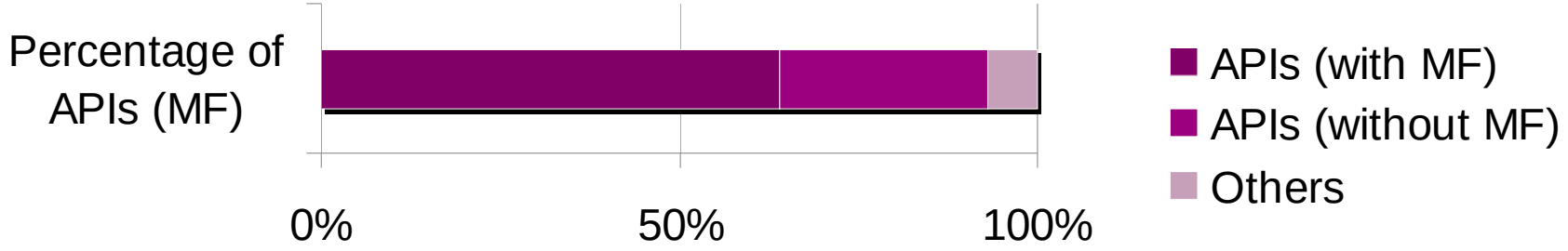
- Domestic manufacturing sites

  Domestic manufacturing sites: Approximately 500

  - Sites inspected by the PMDA (facilities licensed by the Minister): 135
    Biological products: 116
    Radiopharmaceuticals: 19
  - Sites related to new drugs (facilities licensed by the prefectural governor; sterile drugs, general, etc.): Approximately 350 (approximate figure)

5. Problems in GMP control
(Marketing authorization holder/in-country caretaker of MF)

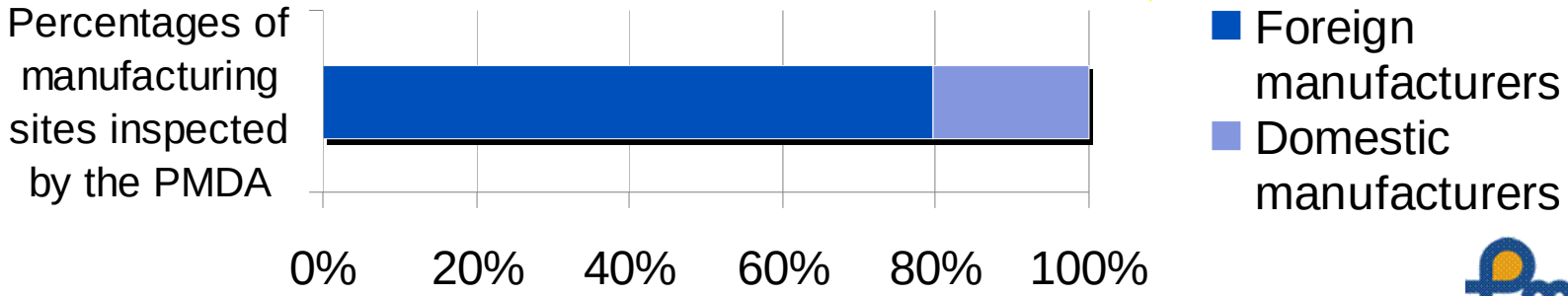
The percentages of APIs, etc. in inspections for renewal of GMP certificates (periodic) by the PMDA



A majority of the inspections are through in-country caretakers of MF

From the last slide (No.27):
Percentage of foreign manufacturing sites in GMP inspections

80 %



5. Problems in GMP control
(Marketing authorization holder/in-country caretaker of MF)

Problems with in-country caretakers

- Lack of communication
  - In-country caretakers sometimes do not correctly understand the actual situation of manufacturing control and quality control. Therefore, the situation is not reflected in the MF.
  - Changes in a manufacturing site are sometimes not conveyed to the in-country caretaker of MF in a timely manner.
  - Lack of explanation to the manufacturing site about the pharmaceutical regulations in Japan.
- Lack of knowledge of the pharmaceutical regulations, GMP control, manufacturing technologies, and/or science

5. Problems in GMP control
(Marketing authorization holder/in-country caretaker of MF)

Problems with marketing authorization holders

- <u>Lack of capability to manage suppliers</u>
  - Marketing authorization holders sometimes do not understand the situation of GMP control at the manufacturing site and do not carry out GMP audits there themselves, leaving the audit to the in-country caretakers of MF.
  - Persons conducting the GMP audit at the manufacturing site do not have sufficient knowledge of pharmaceutical regulations, GMP control, manufacturing technology and/or science.
  - In some cases, a manufacturer is not properly selected in accordance with the GMP standard.
  - Insufficient guidance on GMP controls through supplier audits for the manufacturing site.

5. Problems in GMP control
(Marketing authorization holder/in-country caretaker of MF)

Issues to be considered

- **Properly organize the supply chain**
  - ✓ Collaboration among all parties, including **the manufacturing site, in-country caretaker, marketing authorization holder**, and trading companies, who are engaged in processes from manufacturing to marketing of the drugs.
  - ✓ It is critical to carry out continuous activities to improving GMP control at the manufacturing site. **Management of and the giving instructions to the manufacturing site by the marketing authorization holder should be improved.**
- **Improve scientific knowledge**
  - ✓ The situation related to the methods of manufacturing control and quality control should be understood correctly and scientifically, and potential problems should be identified so that proper action can be taken to correct them.

★ Marketing authorization holders and manufacturers are parties who have legal responsibilities and might be subjected to administrative dispositions.

However,

care by all the parties involved in the supply chain is indispensable for delivering high-quality drugs to patients.

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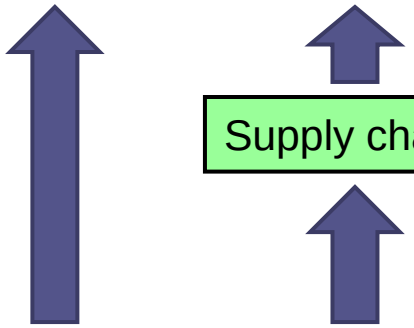
— High-quality drug products for patients (Safe products and stable supply) —



Supply chain: The role of each entity is important.

Total lifting of the contract drug manufacturing ban. Borderless distribution.

Marketing authorization holders have important roles and responsibilities in controlling the supply chain.

Marketing authorization holders are requested not to rely solely on in-country caretakers of MF and personnel at the manufacturing sites, but to make agreements with manufacturers according to the GQP ministerial ordinance (Article 7), ensure proper manufacturing control and quality control, by means such as direct audit of manufacturers (Article 10), and to supervise and manage the manufacturers.

Marketing authorization holders are requested to take proper leadership, control the supply chain, and select appropriate companies.

Thank you for your attention

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