PMDA GMP Inspection

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Incorporated Administrative Agency –

The Pharmaceuticals and Medical Devices Agency (PMDA).

Today's Content

- Outline of Overseas On-Site inspections
- Procedure for Decision of an On-site inspection
- Discrepancy/Inconsistency in Desktop/Questionnaires inspection
- Cases of GMP Non-compliance
- (Reference)
  Cases indicated when on-site inspections were made at Indian manufacturing sites

Outline of Overseas On-Site inspections

Number of Manufacturing Sites, which are subject to PMDA's inspection

As of March 2012

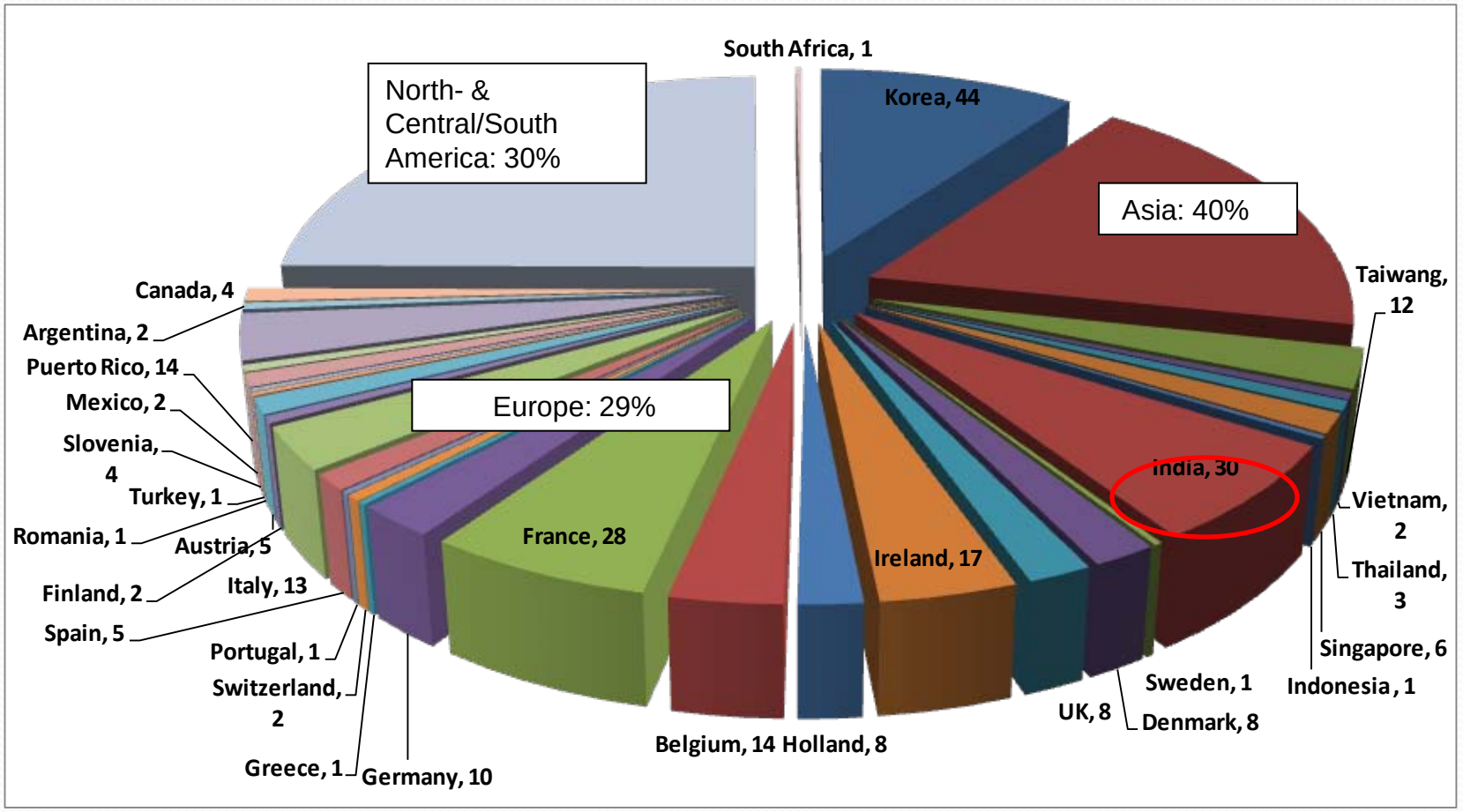
- **Overseas Manufacturing Sites**
  - Accreditation-obtained sites: 2385
    Asia/Middle East: 941 (Drugs: 801, Quasi-drugs: 140)
    Europe: 983 (Drugs: 914, Quasi-drugs: 69)
    North-America, Central/South America, Africa and Oceania: 461
    (Drugs: 398, Quasi-drugs: 63)
  - Manufacturing sites with no accreditation required
    (Bulk drug intermediates, (Rx-to-) OTC switched bulk drugs, etc.): about 300 (appropriate figure)

Overseas mfg. sites: about 2,700

- **Domestic Manufacturing Sites**
  - PMDA is an inspection Authority (Minister-designated facilities): 135
    Biological Products, etc.: 116
    Radioactive Products: 19
  - New drugs-related Products
    (Governor-approved sterile, general drugs, etc.): about 350 (appropriate figure)

Domestic mfg. sites: about 500

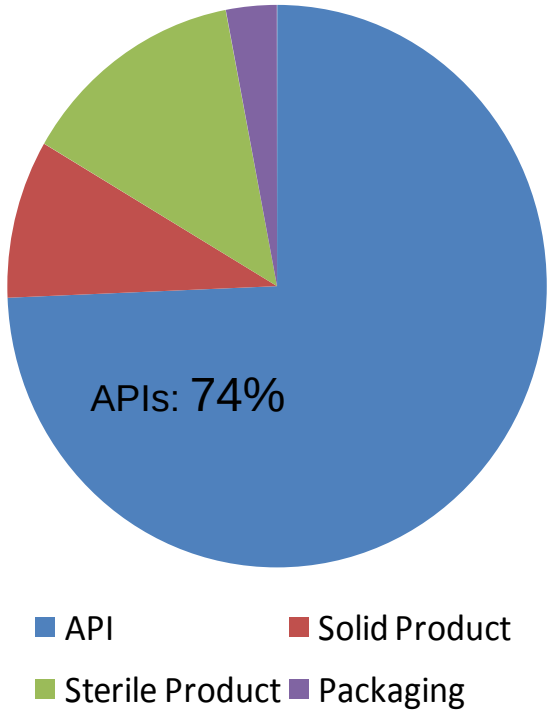
Number of Overseas inspections on a country-by-country basis



Performed from April 2005 though March 2012
(No. of Manufacturing Sites: 438 in 32 countries)

Outline of GMP inspections by Region and by Field Pertaining toEthical Generic Drug Products (From April 2006 through March 2012)

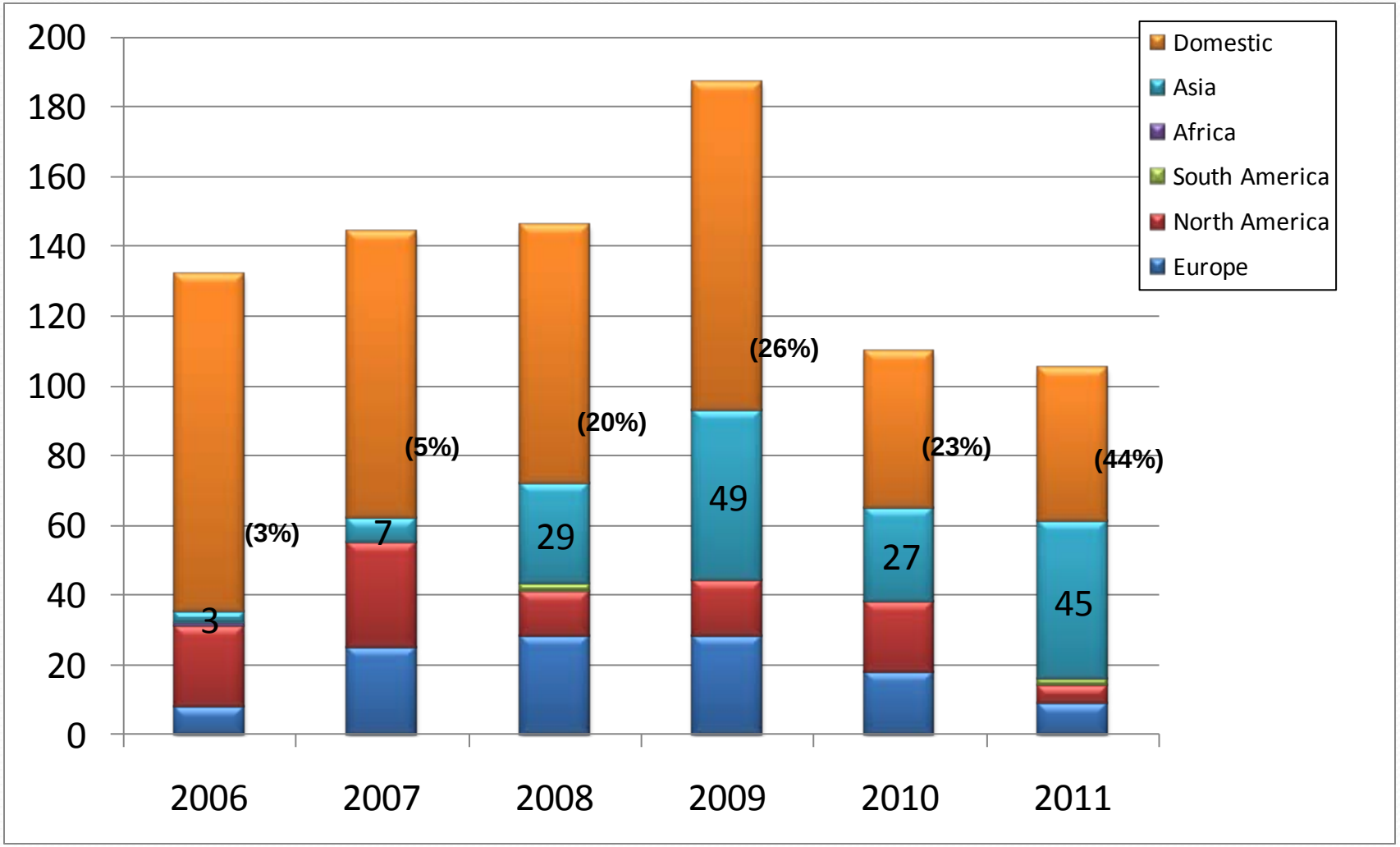
分野	EU	North America	Central/South America	Asia	Others	Total
Sterile Products, Bio-Pharmaceuticals	70	8	4	38	8	128
Solid Drug Products	24	0	0	59	3	86
APIs	213	25	3	462	1	704
Packaging & Test laboratory	13	4	3	7	2	29
Total	320	37	10	566	14	948



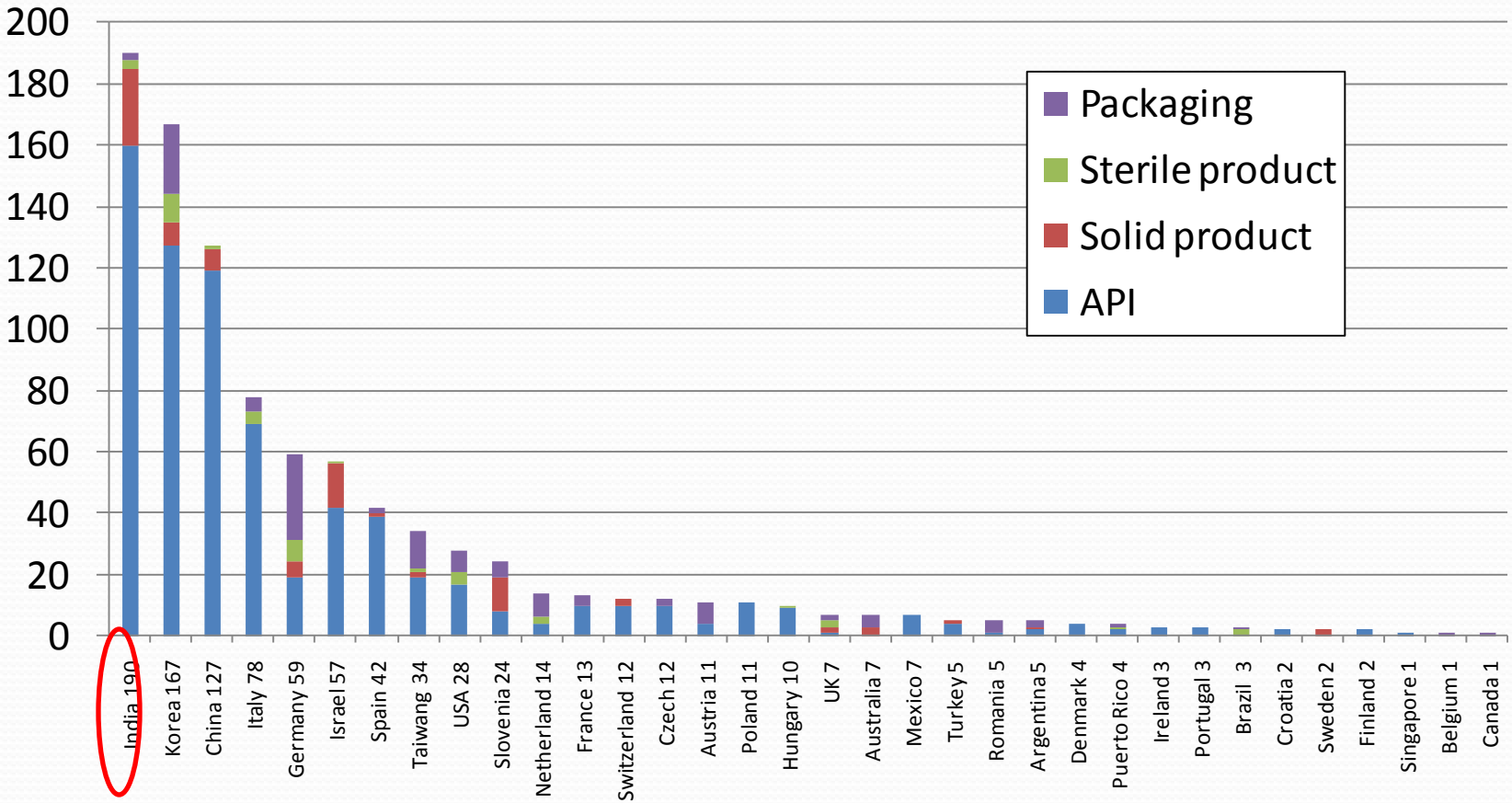
Bulk pharmaceutical chemicals/APIs account for 74% of the total, and among them Asia accounts for more than 60% of the BPCs.

Number of Domestic and Overseas On-Site inspections/Annual Transition of inspections by Region over the years

(from April 2006 through March 2012)



GMP inspection (By Country) for Ethical Generic Drugs
(From April 2006 through March 2012)



Bulk Pharmaceutical Chemicals (BPCs): India, Korea, China, Italy, …

Grading of 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

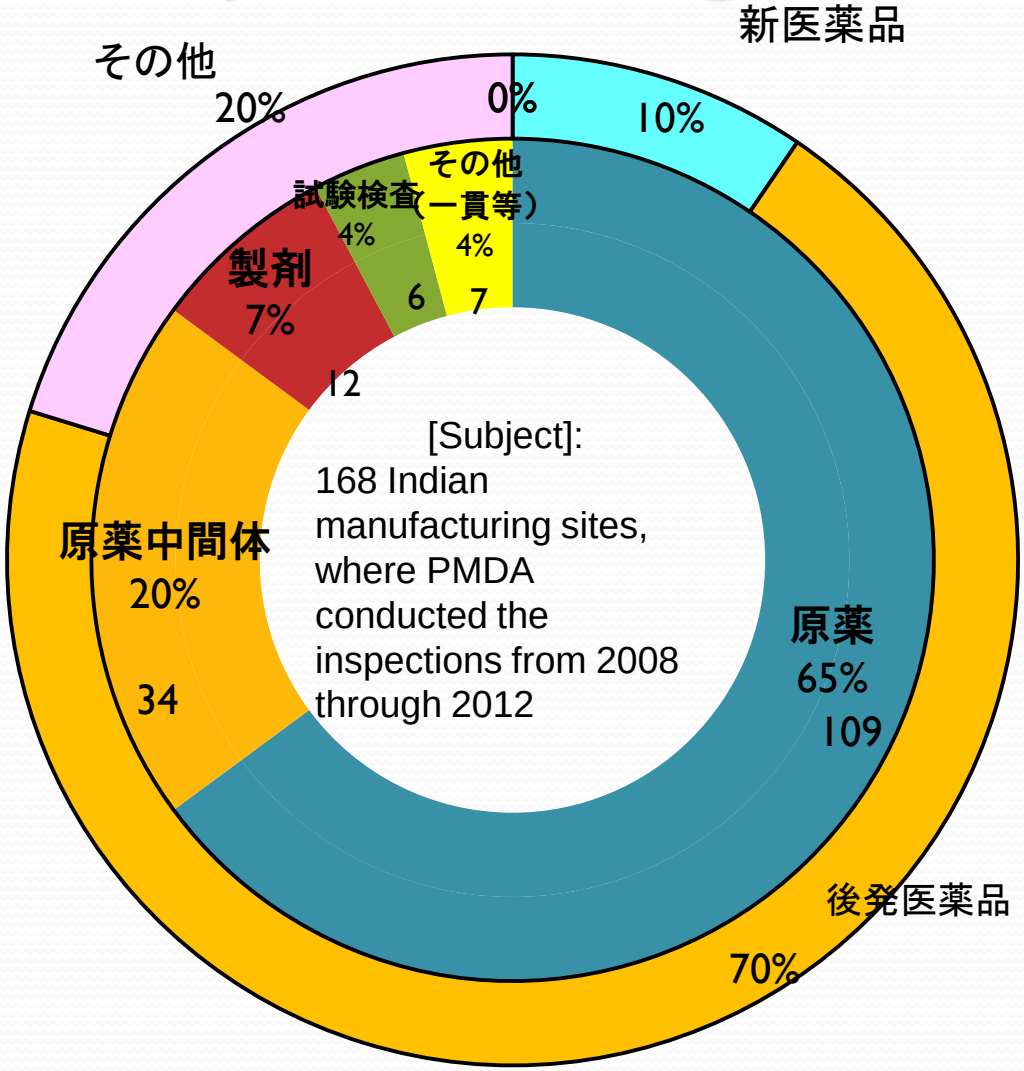
Main region	Number of on-site inspection (2007.12 – 2012.10)	Mfg. site classification		Total	(C+ D) ratio (%)
		C	D		
Asia (except Japan)	181	50(12)	5(3)	55	30%
EU	102	4(2)	0	4	4%
North America	66	5(1)	1(1)	6	9%
Central/South America	13	2(1)	0	2	15%
Japan	348	58(19)	5(5*)	63	18%

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

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

Strengthen the surveillance system

Indian Manufacturing Sites with inspections being conducted by PMDA



【Details of manufactured items】

Others (consistent, etc.): 20%,

New drugs: 10%,

Testing: 4%,

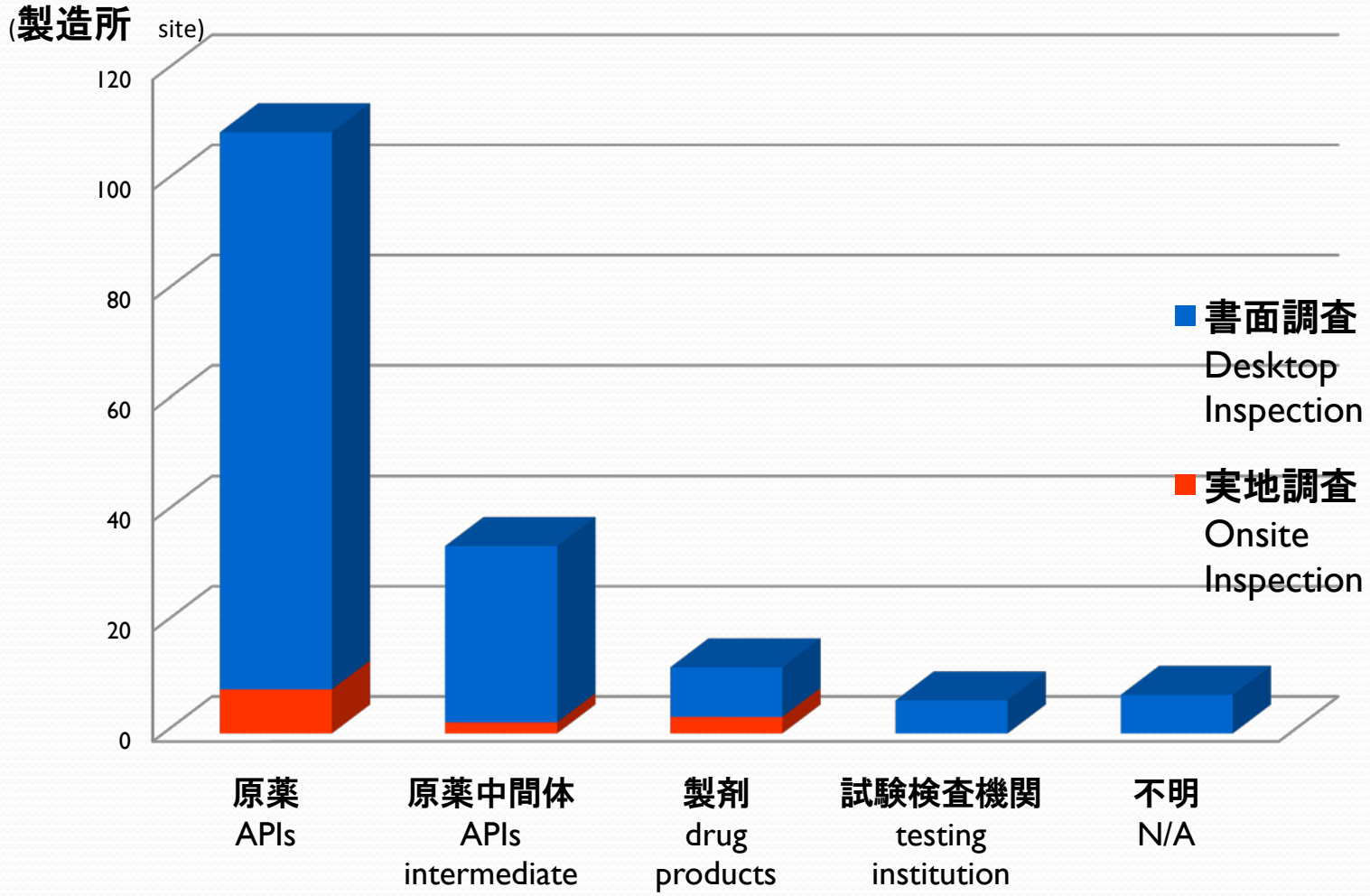
Drug products: 7%

APIs intermediates: 20%,

APIs: 65%,

Generic drugs: 70%

Indian Manufacturing Sites where PMDA conducted the inspections



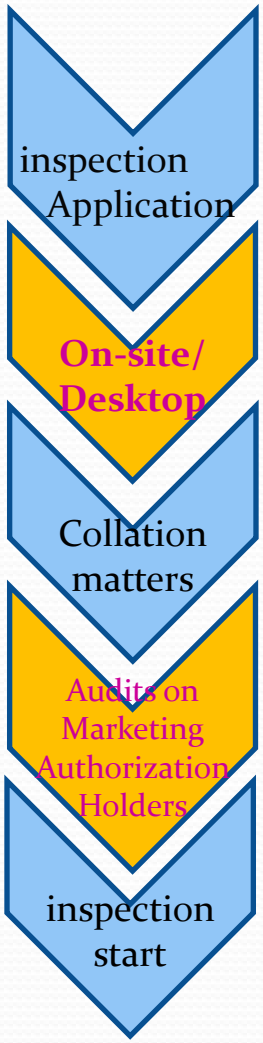
Grading Assessment of Manufacturing Sites by On-site inspection

(Collected by the number of manufacturing sites but not by the number of application)

A評価 Grade A	4
B評価 Grade B	6
C評価 Grade C	2
D評価 Grade D	1
計 Total	13

Procedure for Determining an On-Site inspection

From inspection Application to inspection Initiation



- **Outline of inspection-subject product item in the manufacturing site: Form1**
- **Outline of Drug Product Manufacturing Site (for Foreign Manufacturing Site): Form3**

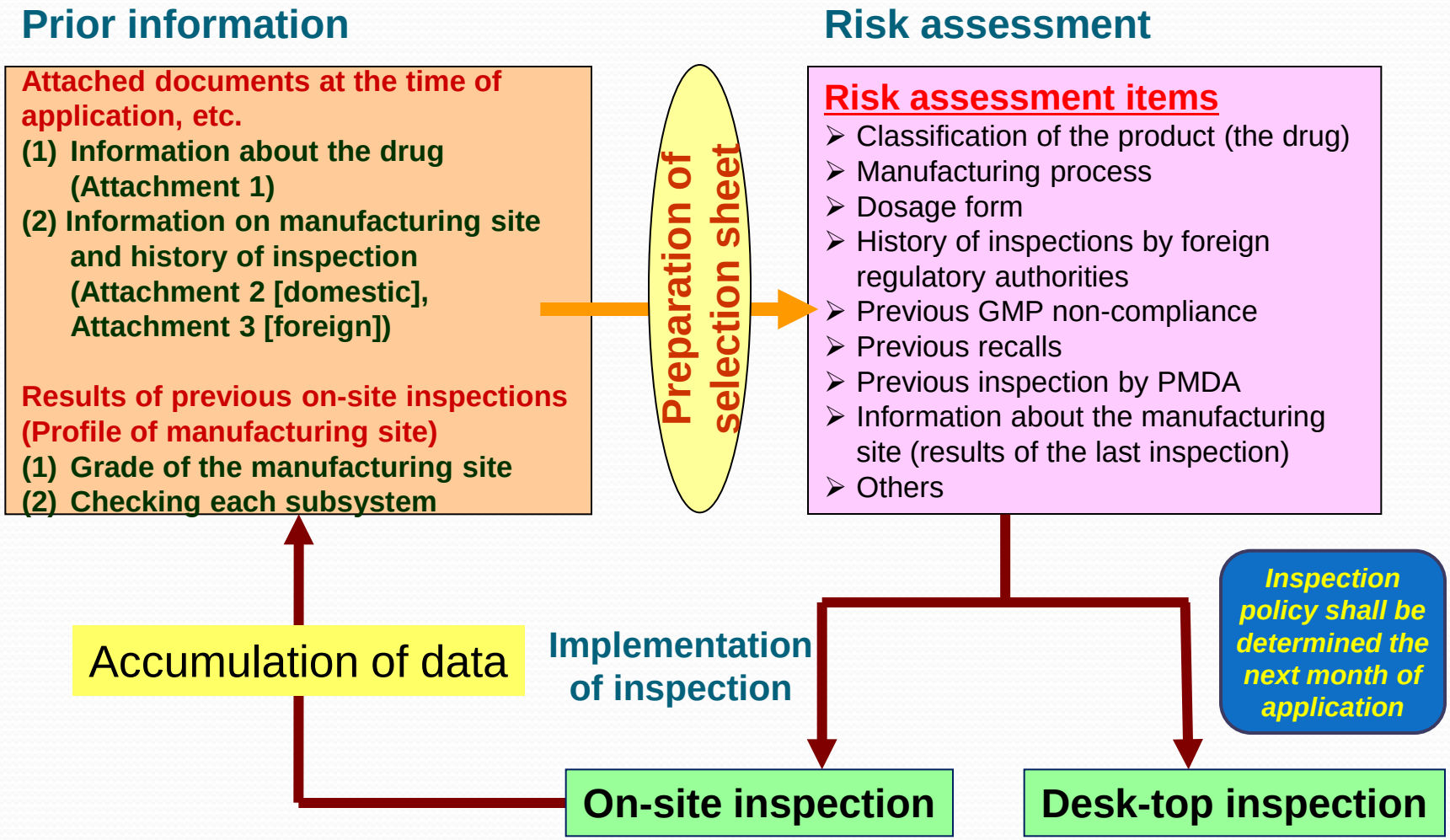
- **Risk Assessment**
- **Determination of inspection procedure**

- **On-site inspection: Adjustment of schedule → Documents submitted in advance**
- **Desktop inspection: inspection data**

- **Whether some discrepancies exist or not**
- **Verification of GMP conformity**

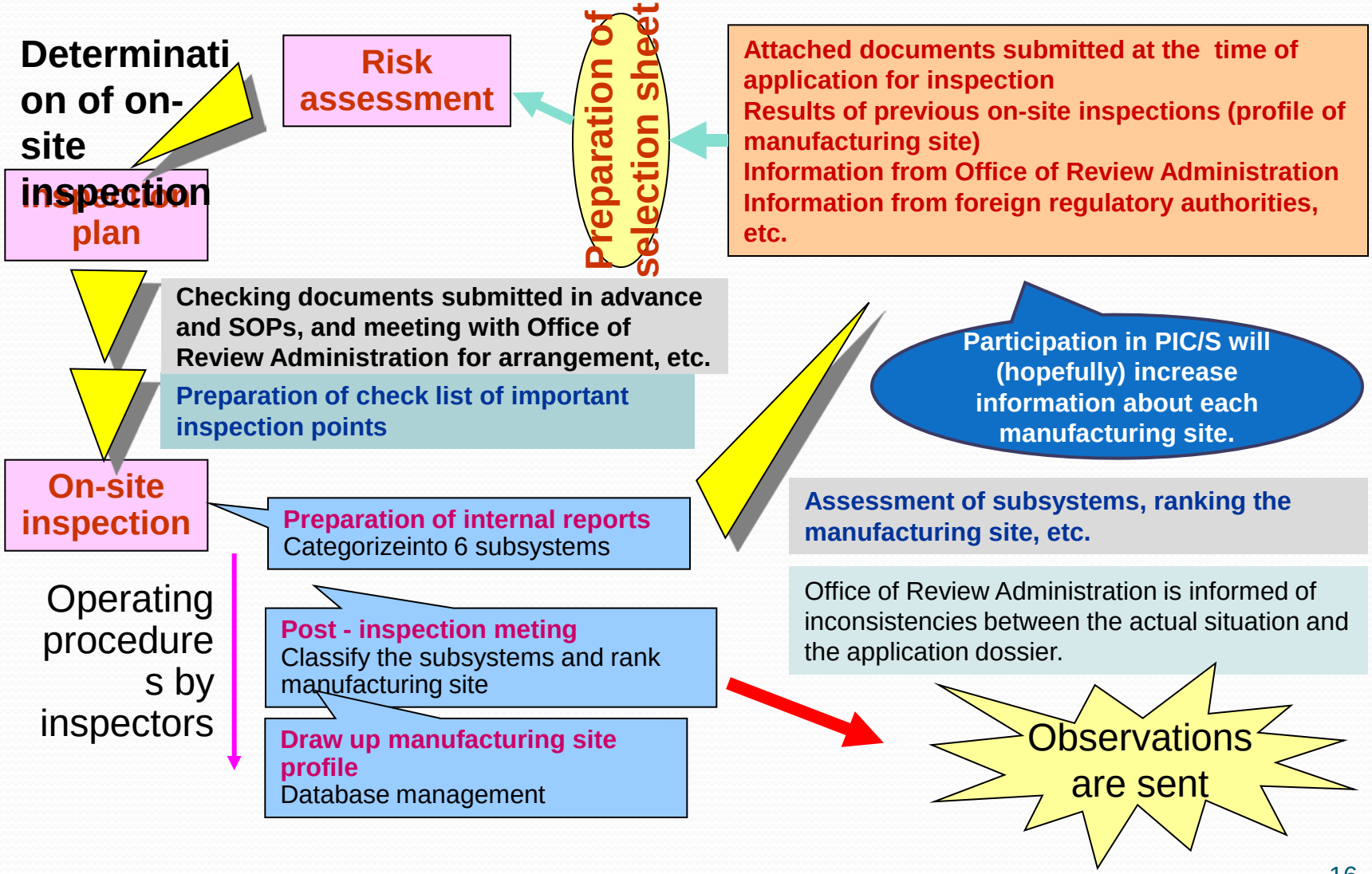
- **On-site inspection: Indicated matters and the grading of the manufacturing site**
- **Desktop inspection: Confirmation by written inquiry**
- **Existence/non-existence of Discrepancies**

Selection of inspection sites according to risks



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

Decision-making cycle for inspection policy



Outline of Drug Manufacturing Sites

(Notice dated October 27, 2010)

様式３
Form 3

医薬品製造所概要（外国製造所用）

Outline of Drug Manufacturing Site

(Foreign Manufacturing Site)

平成　年　月　日現在
As of MM/DD/YY

製造所名 Name of manufacturing Site	
所在地 Address	
国内連絡先 Contacts in Japan	業者名 Name of the company_____ 担当者 Contact person_____ 電話 Phone_____ FAX_____ E-mail_____

認定番号 Accreditation No.	当初認定年月日 Date of initial accreditation
認定の期限 Expiry date	認定の区分 Accreditation category

従業員数（パート社員等も含む）Numbers of employees (including part time employees)

全従業員数 人 Total	製造部門 人 Manufacturing department	QC 部門 人 QC	QA 部門 人 QA

製造所の責任者 Responsible person of the Site
(Qualified person in the EU, or head of quality unit in other countries)

氏名 Name	職名 Job title
電話 Phone_____ E-mail_____	FAX_____

Outline of Drug Manufacturing Sites (Continues)

製造品目数（日本への輸出品目数は（ ）で記載）
Number of manufactured products (Number of products exported to Japan should be described in parenthesis)

	原薬・中間体 Manufacturing of APIs/Intermediates	製剤化工程 Manufacturing of drug Products	一次包装工程以降 After primary packaging	二次包装工程以降・表示・保管のみ Secondary packaging・Labeling・Storage
製造品目数 Number of products				
高生理活性物質 High pharmacological active substances				
ペニシリン系抗生物質 Penicillin antibiotics				
βラクタム系抗生物質 β-lactam antibiotics				

注）1．高生理活性物質とは、ある種のステロイド類、細胞毒性のように強い薬理作用又は毒性を有する物質等をいう
2．原薬の小分けは、原薬・中間体の欄に記載
Note) 1. High Pharmacological active substances(e.g. certain steroids or cytotoxic substances)
2. In cases of subdividing manufacture of APIs, please fill in the Manufacturing of API/Intermediate column.

Outline of Drug Manufacturing Sites (Continues)

施設情報 ①
Information of the manufacturing site I

製造所敷地面積 Area of the site	倉庫面積 Area of the warehouse
製造施設面積 Area of the manufacturing facilities	試験検査施設面積 Area of the testing laboratory

施設情報②（使用している重要なコンピュータ化システム）
Information of the manufacturing site II
(Overall function of major computer system adopted in the manufacturing site)

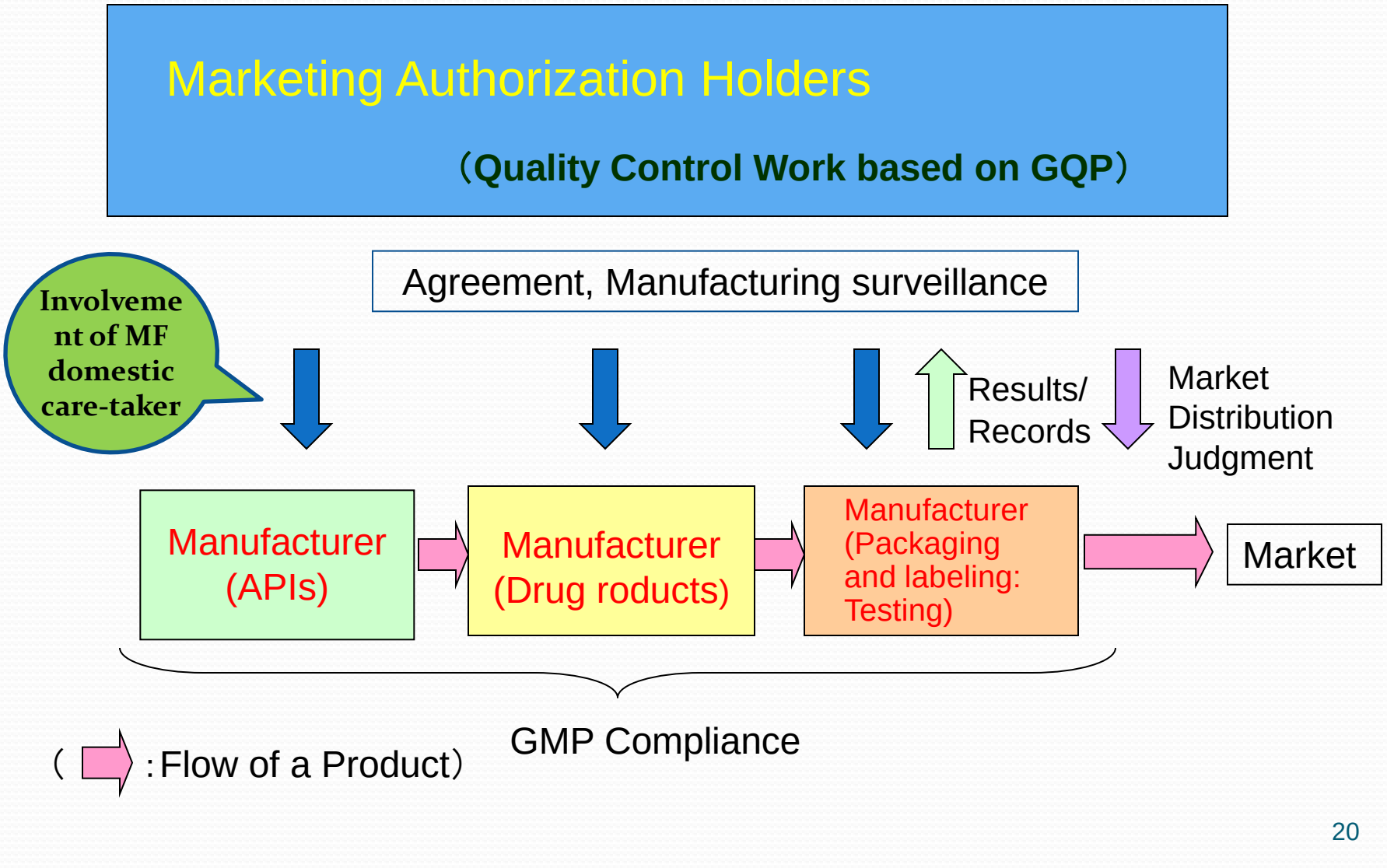
重要なコンピュータ化システムの名称 Name of major computer system	□ERP □MES □LIMS □DCS □その他 Others （ ） □使用なし(N/A)

過去５年間の行政機関からの査察の有無
History of GMP inspections by regulatory authorities over the past 5 years.

行政機関名 Name of regulatory authorities	時期 Inspection date	対象品目名 Name of inspected products	結果 Inspection results	実地か書面かの別 Type of inspection (On-site/Desk-top)

過去５年間の回収、GMP 不適合の有無（有の場合は概要を記載）
History of product recall or GMP non-compliance over the past 5 years (Please specify details.)

Agreement on GQP and Quality



From the Preliminary inspection of Marketing Authorization Holders

- **There were no records on the manufacturing control and quality control.**
- **There was no manufacturing facility necessary for the inspection-subject product item.**
- **No manufacturing activity was done at the inspection-subject manufacturing site.**
- **GMP control was non-conforming.**

Discrepancy/Inconsistency in Desktop inspection

Major Deficiency for Descriptions in Master File (MF)

- Discrepancy in actual manufacturing method/Specification, etc.
- Omission of description of manufacturing facilities, etc.
  - API intermediate and crude API were manufactured in another manufacturing site.
  - Outside contract testing institutions, and a facility with only pulverization process.
- The manufacturing method has been changed.
  - Change registration/minor change notification were not made.

The Causes (1) for Deficiency in Descriptions in MF

- The MF in-country caretaker responded to written inquiries on his/her own judgment without communicating to the manufacturing site.
- Since there were multiple overseas agents who had a connection between the MF in-country caretaker and the manufacturing site, the MF in-country caretaker was unable to communicate directly to the manufacturing site.
- The MF in-country care-taker has made the maintenance of the MF (Description arrangement/Change registration/Minor change notification) based on the old information he/she obtained in the past.

The Causes (2) for Deficiency in Descriptions in MF

- The MF number, which was quoted to the application document for market authorization of a drug (product), was wrong or inappropriate.
- The inquiry content from the PMDA was not correctly conveyed to the MF Registrant (the manufacturing site).
- The MF in-country caretaker could not deal with to the Conformity inspection, and thus he was replaced with another MF in-country caretaker in a hurry.
- The descriptions in the MF were inappropriate, such as too simplified content.

MF Registrant (Manufacturing Site) and MF In-Country Caretaker

Article 72, Second Clause of Enforcement Regulations of the Pharmaceutical Affairs Law

A person manufacturing APIs, etc. in a foreign country intends to make application of the registration specified in the preceding clause shall appoint at the time of the application a person who is engaged in **deskwork services of the registration, etc.** in Japan (hereinafter referred to as "DMF registered in-country caretaker, etc.") from among the persons who reside in Japan (including a representative in case of a foreign corporation with office in Japan).

- The MF registrant shall appropriately disclose information to the MF in-country caretaker.
  - According to the agreement with the marketing authorization holder, necessary information (Quality information, change, deviation).
  - Via the MF in-country caretaker, disclose minimum necessary information to the marketing authorization holder.
- The MF in-country caretaker shall deal with the pharmaceutical affairs on behalf of the MF registrant.
  - A relationship with the MF registrant to exchange information periodically.
  - Based on the information from the MF registrant, deal with the pharmaceutical affairs.

Cases of non-compliance in recent GMP compliance reviews

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.*

Non-Compliant 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.

Non-Compliant 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.

Non-Compliant 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.

Thank you very much for your attention!