Package insert notification system

PMDA/MHLW

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Background of the package insert notification system

"Review on the Pharmaceutical Administration to Prevent Recurrence of Yakugai (Drug-induced suffering) (first proposal)" (April 30, 2009)
Committee for Investigation of Drug-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Recurrence of Yakugai Similar Sufferings

It was suggested that the positioning of package inserts at the time of approval, such as inclusion as an approval item should be reviewed taking account of European and American systems, and the government's responsibilities should be clarified by deeming them as official documents.

"Summary on System Reform of Pharmaceutical Affairs Act etc." (January 24, 2011)
Subcommittee of Pharmaceutical System Reform of the Health Sciences Council

- It was found that the government's regulatory power for the positioning of package inserts should be clarified in the Pharmaceutical Affairs Act in light of their importance. As the method, whether the package insert should be subject to approval or an obligation to notify should be imposed on companies was discussed.
- At the discussion, if approval was required, a concern about contracting medical practices was pointed out, and the opinion that it would be appropriate to review a system to impose on marketing authorization holders (MAH) an obligation to make prior notifications of package inserts before the start of marketing and at the time of their revisions was dominant.

In consideration of the summary, the package insert notification system is to be introduced in the Amendment Act.

Package insert notification-related clauses (Article 52-1)

(Package insert and other information)

Article 52 In the document attached to pharmaceuticals or on its container or closure (hereinafter referred to as the "package insert etc." in this article), the following items shall be indicated (referred to as "package insert and other information" in the next paragraph and article) based on evidence obtained from the latest literature and other sources on the concerned pharmaceuticals with the proviso that exemptions may be established as specified by the Ordinance of the Ministry of Health, Labour and Welfare (MHLW):

1 Dosage and administration, or other necessary precautions for use and handling

2 For pharmaceuticals included in the Japanese Pharmacopoeia (JP), the information specified by the JP to be presented in the package insert etc.

3 For *in vitro* diagnostics for which their standards have been stipulated by the provisions of Article 41-3, the information required by the standards to be presented in the package insert etc.

4 For pharmaceuticals for which their standards have been stipulated by the provisions of Article 42-1, the information required by the standards to be presented in the package insert etc.

5 In addition to the information set forth in the preceding items, any items specified by the MHLW Ordinance.

Package insert notification-related clauses (Article 52-2)

(Package insert and other information)

Article 52

2 In the case where a proprietor of a pharmacy, MAH or manufacturer of pharmaceuticals, or wholesaler sells or gives *in vitro* diagnostics to a pharmacist, proprietor of a pharmacy, MAH or manufacturer of pharmaceuticals, wholesaler, physician, dentist, veterinarian, or proprietor of a hospital, clinic or veterinary clinic, when selling or giving them, notwithstanding the provisions of the preceding paragraph, it shall not be required to indicate the package insert and other information in the package insert etc. of the in vitro diagnostics if it falls under both of the following items:

1 When the MAH of the in vitro diagnostics provides the package insert and other information of the *in vitro* diagnostics through means using an electronic data processing system or other information-communication technologies specified by the MHLW Ordinance; and

2 When a person who intends to sell or give the *in vitro* diagnostics has received approval from a person who intends to purchase or get the *in vitro* diagnostics for which there is no indication of the package insert and other information in the package insert etc. as stipulated by the MHLW Ordinance.

Package insert notification-related clauses (Article 52-2)

(Notification of package insert and other information)

Article 52-2 When marketing pharmaceuticals designated by the Minister of Health, Labour and Welfare, a MAH of pharmaceuticals shall notify beforehand the Minister of Health, Labour and Welfare about precautions necessary for use and handling and other information stipulated by the MHLW Ordinance among the package insert and other information of the pharmaceuticals, as specified by the MHLW Ordinance. This shall also be applied when revising the said precautions and other information.

2 When the notification pursuant to the provision of the preceding paragraph was made, a MAH of pharmaceuticals shall immediately publish the package insert and other information of the pharmaceuticals through means using an electronic data processing system or other information-communication technologies specified by the MHLW Ordinance.

Products subjects to the package insert notification system

- **Drugs and medical devices designated by the Minister of Health, Labour and Welfare pursuant to the provisions of Article 52-2-1 and Article 63-3-1 of the Act for Ensuring etc. the Quality, Efficacy and Safety of Drugs, Medical Devices, etc. (MHLW Announcement No. 320, 2014)**

	Applicable products	Non-applicable products
Drugs	• Ethical drugs (pharmacy drugs) However, excluding the following: (• *In vitro* diagnostics • Drugs not requiring approval • Pharmacy-compounded drugs) • Guidance-mandatory drugs	Over-the-counter drugs Exceptional products listed in the left column
Medical devices	Class IV medical devices	Classes I to III medical devices
Regenerative medical products	All products	—

* All regenerative medical products are subject to the said system pursuant to the provisions of the Act.

Items required to be notified (For ethical drugs)

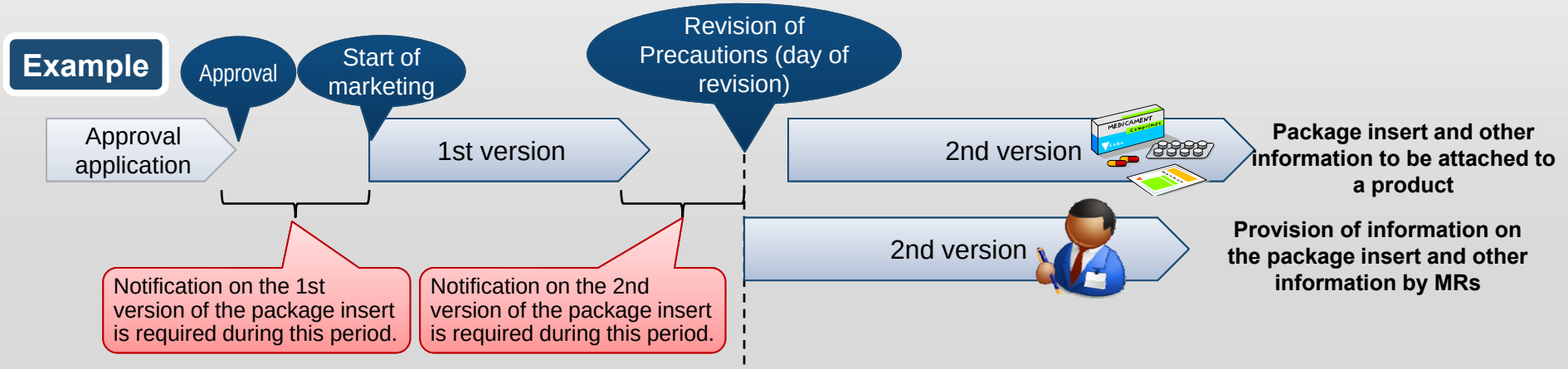
- **Items required to be notified are "Name" (brand name) and "Precautions necessary for use and handling"**
  (Articles 216-6, 227-4 and 228-7 of the Ministerial Ordinance for Enforcement).
  - **"Precautions necessary for use and handling" refer to information required to be presented in the package insert that is listed and underlined below (PFSB/SD Notification No. 0901-01 dated September 1, 2014 by the Director of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW)**

1 Date of preparation or revision
2 Japan Standard Commodity Classification Number
3 Therapeutic category
4 Regulatory classification
5 Name
6 Warnings
7 Contraindications
8 Description
9 Indications
10 Dosage and administration
11 Precautions
- **Precautions related to the indications**
- **Precautions related to the dosage and administration**
- **Careful administration**
- **Important precautions**
- **Drug interactions**
- **Adverse reactions**
- **Geriatric use**
- **Use during pregnancy, delivery or lactation**
- **Pediatric use**
- **Effects on laboratory tests**
- **Overdosage**
- **Precautions concerning use**
- **Other precautions**

12 Pharmacokinetics
13 Clinical studies
14 Pharmacology
15 Physicochemistry
16 Precautions for handling
17 Conditions for approval
18 Packaging
19 References and request for literature should be made to:
20 Name and address of manufacturer or importer

Time when the notification is required

- **The notification is required (1) before the start of marketing (e.g., at the time of new approval) and (2) when revising the package insert and other information.**
- **"When revising" the package insert and other information, it shall be the day when the information on the package insert and other information after revision begins to be provided.**
  - When information on the revised package insert is provided by medical representatives (MRs) or direct mails (DM) before the start of the marketing of a product to which the package insert is attached, the day of provision of information is the starting day.



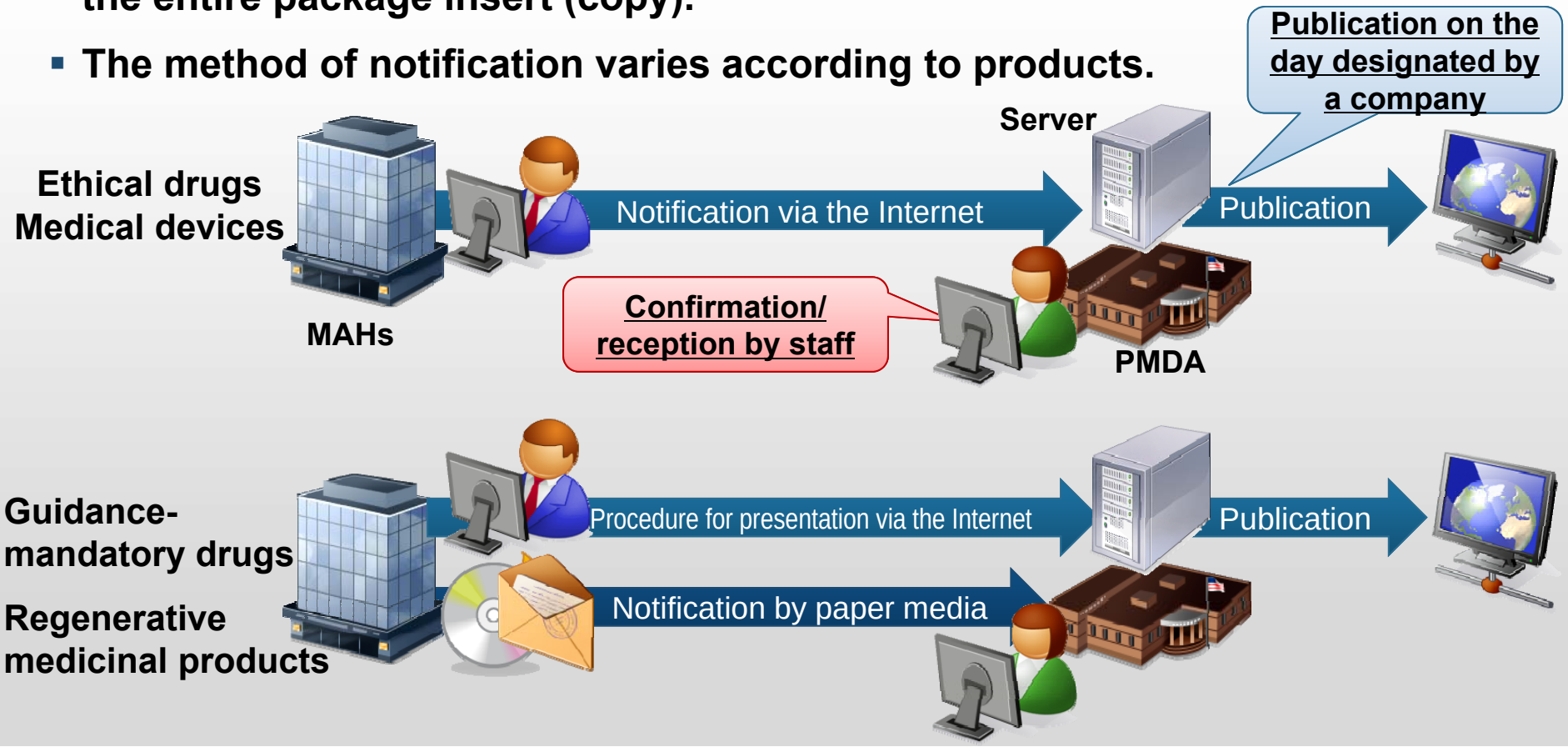
Notification and publication

- **Method for publication should be <u>presented on the website of the PMDA.</u> (Article 216-7 of the Ministerial ordinance for Enforcement)**
  - For ethical drugs and medical devices, a system enabling procedures to be collectively taken for notification and publication is now available.
- **When there is a lag time between the day of notification to the day of actual revision, the information may be published on the day of revision.**
- **For products that have been approved on the day of enforcement, the notification is deemed as being made with the package insert and other information on the website of the PMDA.**
  - The period of the provisional measure for notification of the package insert is only 7 days after enforcement.

<u>For currently marketed products, the said information shall be presented on the website of the PMDA by the day of enforcement to the extent possible.</u>

Method of notification

- **Notification should be made to the PMDA.**
- **It should be made by submitting not only information to be notified but also the entire package insert (copy).**
- **The method of notification varies according to products.**

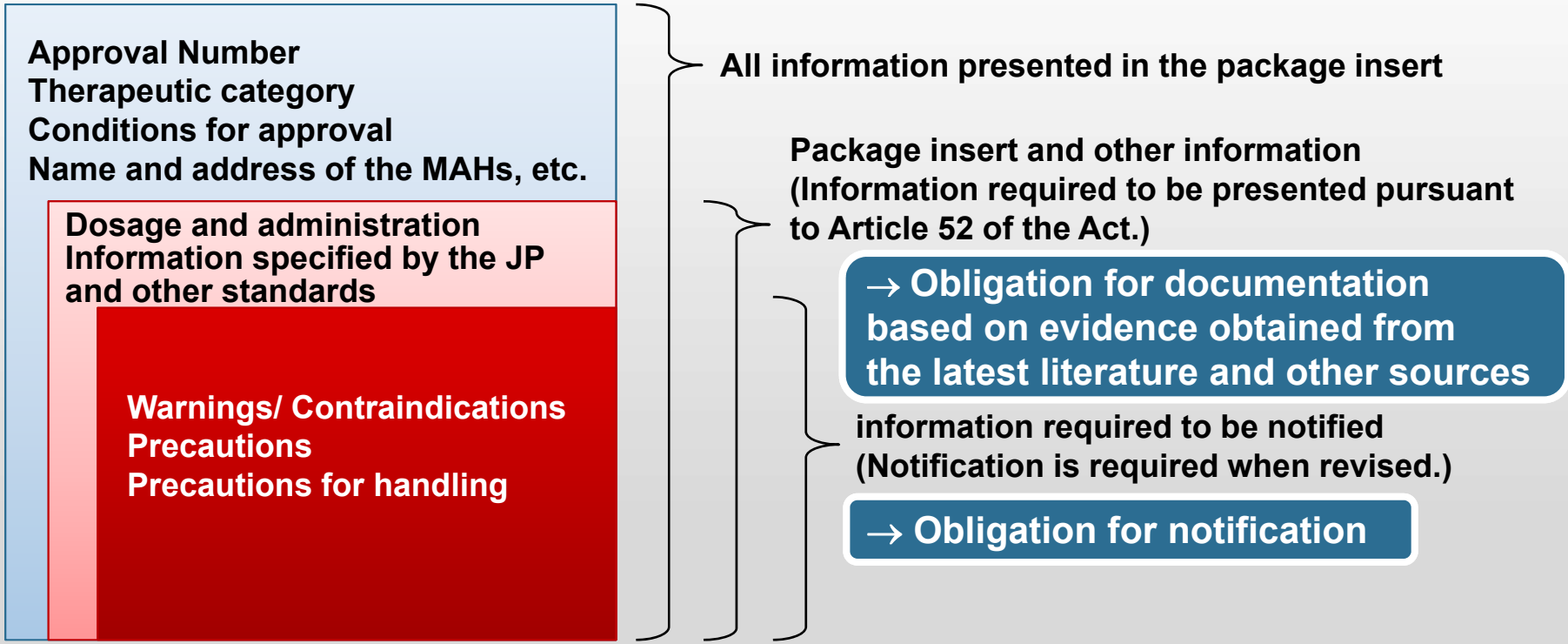


Supplement (in relation to the package insert notification system)

* Administrative Notice "Q&A on notification of the package insert and other information" dated September 1, 2014

In package insert and other information, what is the relationship between the scope of items required to be notified and the scope of information that should be presented based on the latest findings?

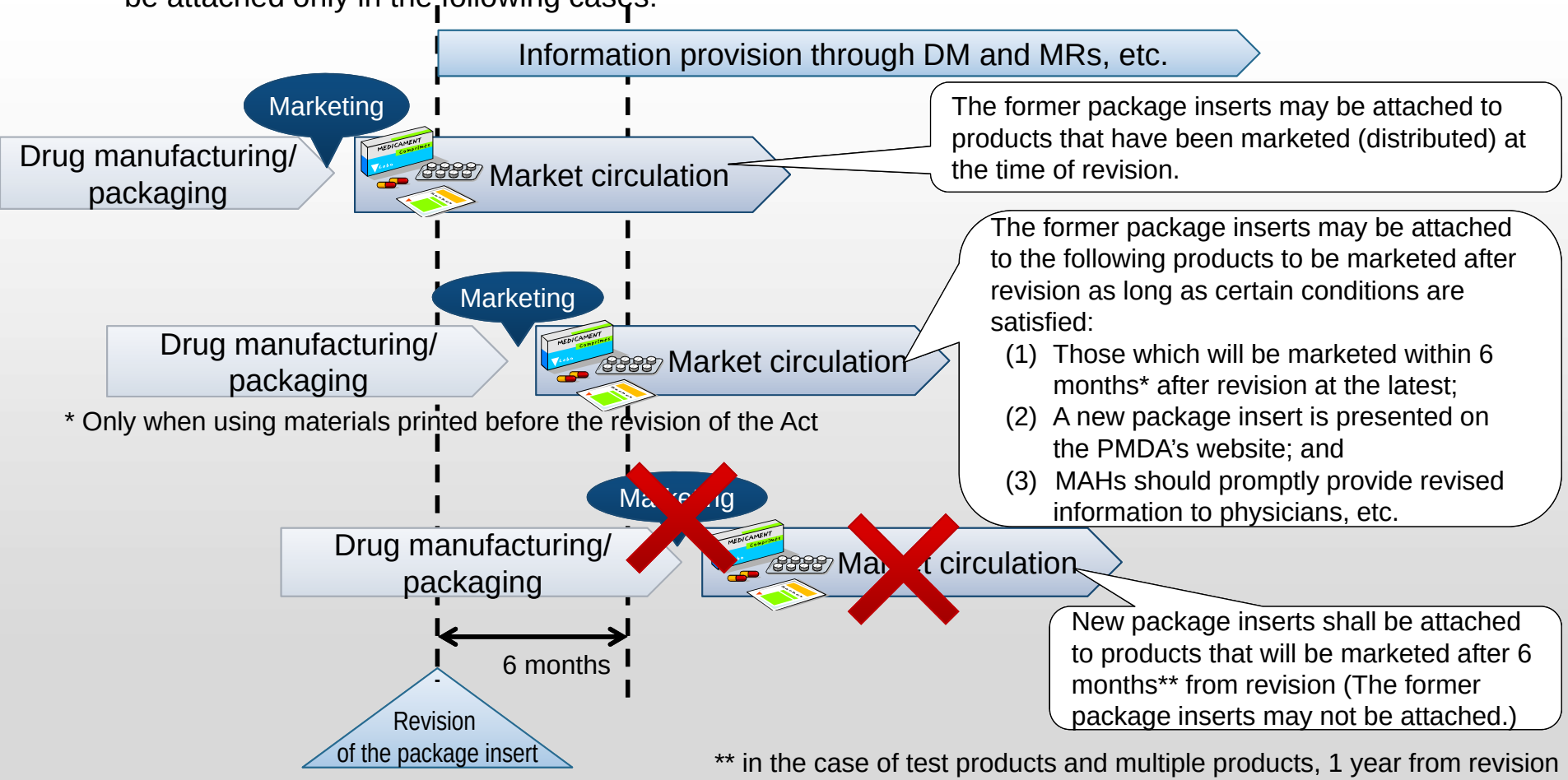
- The arranged results of information are as follows:



Exception for existing products when revising package inserts

Including products not subject to notification

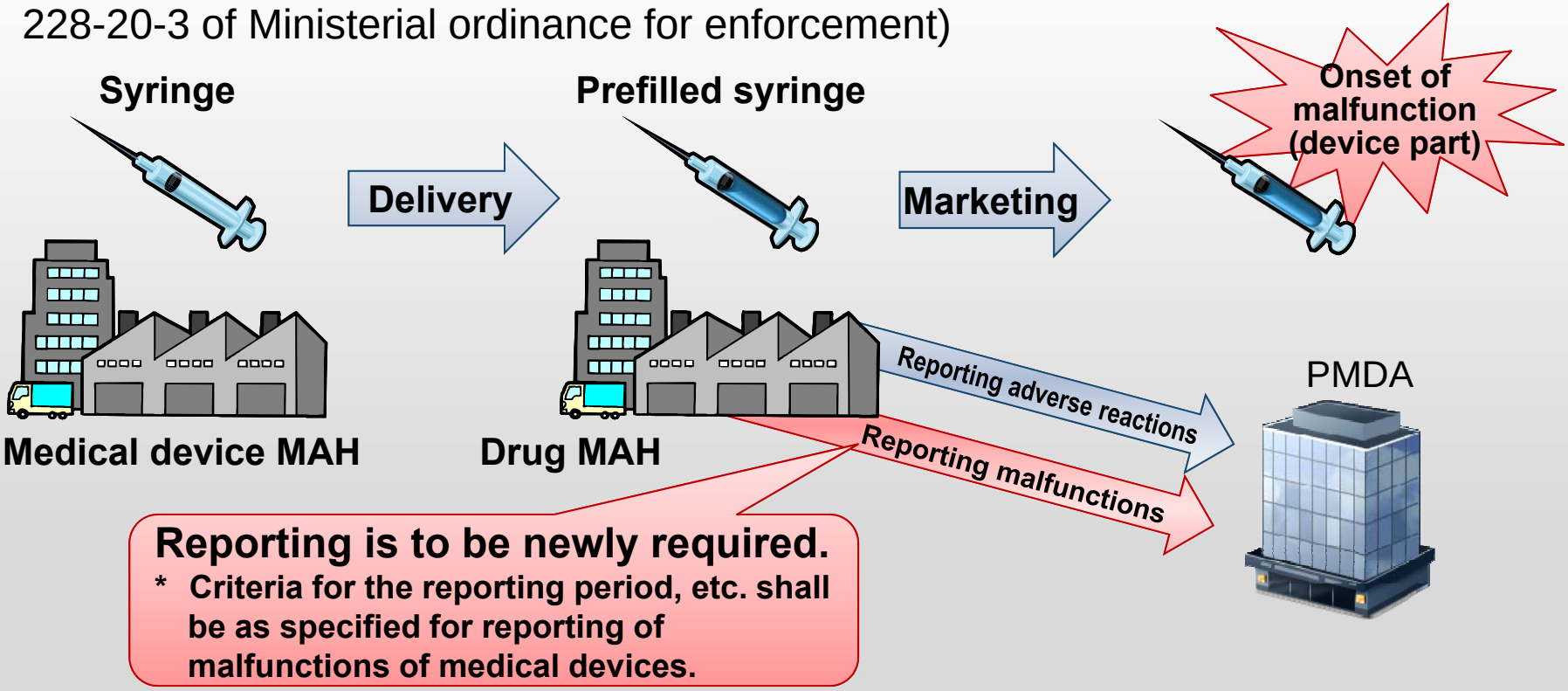
- Package inserts shall be prepared based on evidence obtained from the latest literature and other sources pursuant to the provisions of Article 52-1 of the Act; however, the former package inserts may be attached only in the following cases:



** in the case of test products and multiple products, 1 year from revision

Malfunction reports of combination products (1)

For malfunctions of the device part of a drug approved to be marketed with devices in combination (combination products corresponding to drugs), their reporting was not required; however, with the revision of the Ministerial ordinance for enforcement of the Pharmaceutical Affairs Act, they are now required to be reported as malfunctions from drug MAHs marketing the said products. (Article 228-20-3 of Ministerial ordinance for enforcement)



Reporting is to be newly required.

* Criteria for the reporting period, etc. shall be as specified for reporting of malfunctions of medical devices.

Malfunction reports of combination products (2)

- **Examples of combination products corresponding to drugs**
  - Injections with prefilled syringes, injections with pen-type syringes, etc.
- **Examples of combination products corresponding to medical devices**
  - Drug-eluting stents, heparin-coated catheters, antibacterial agent-containing bone cement, etc.

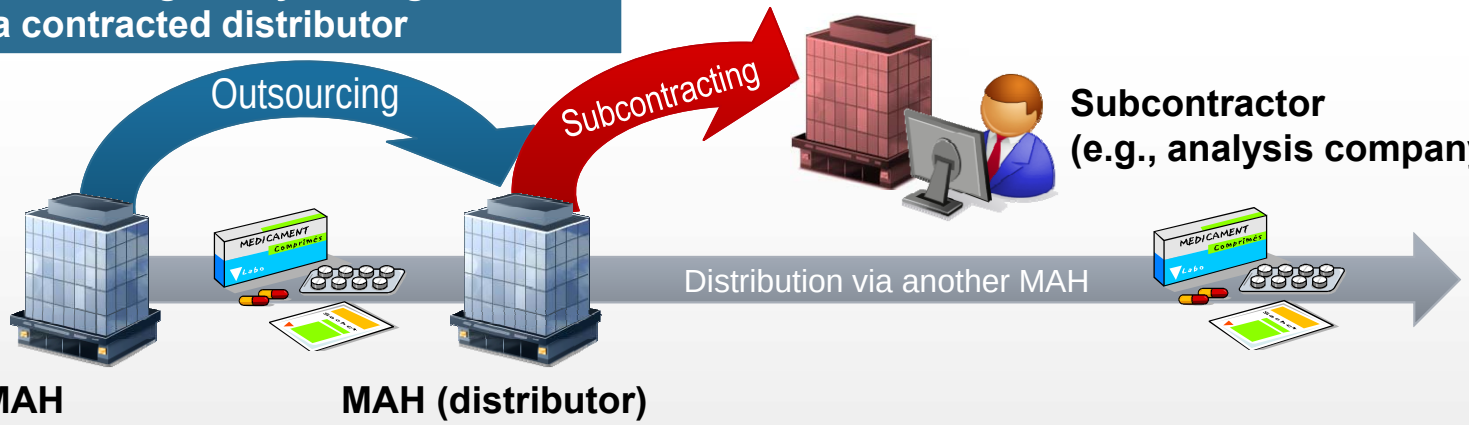
	Adverse reactions etc. associated with drugs present	Adverse reactions etc. associated with drugs not present
Malfunctions of the device part present (including the case where there are health injuries suspected to be attributable to the device part)	Both	Reporting of malfunctions only
Malfunctions of the device part not present	Reporting of adverse reactions only	N/A

- The period of the provisional measure for the application of the provisions for existing products is 2 years. (Obligation for reporting as of November 2016) (Article 7 of the Supplementary Provisions of Ministerial Ordinance on Partial Amendment of the Ministerial Ordinance for Enforcement)

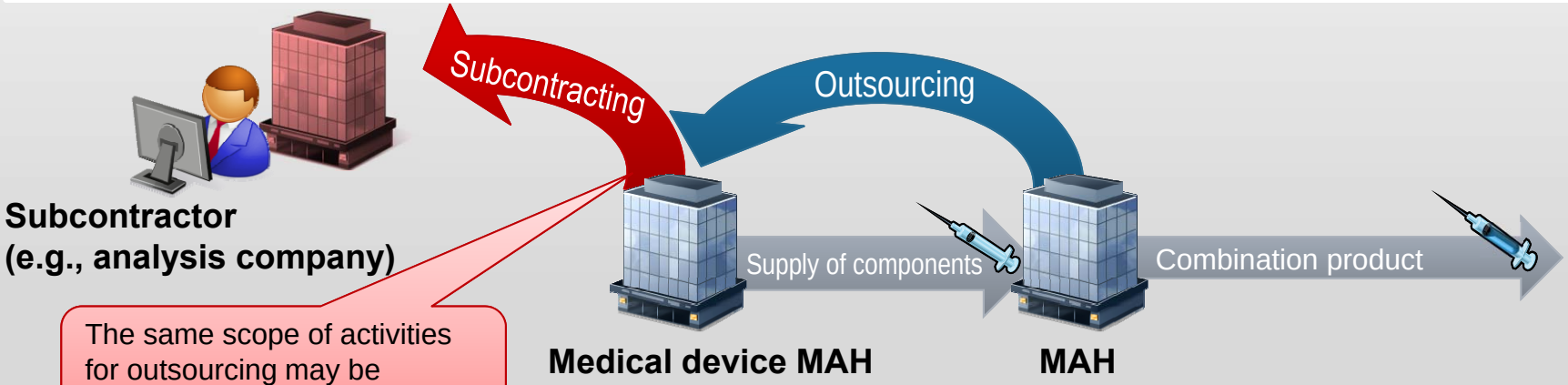
Subcontracting out of safety management activities (1)

・Collection of safety management information
・Analysis of safety management information
・Implementation of safety assurance measures
The above items may only be subcontracted out.

Pattern 1: Outsourcing safety management activities to a contracted distributor



Pattern 2: Outsourcing safety management activities to a medical device MAH for combination products

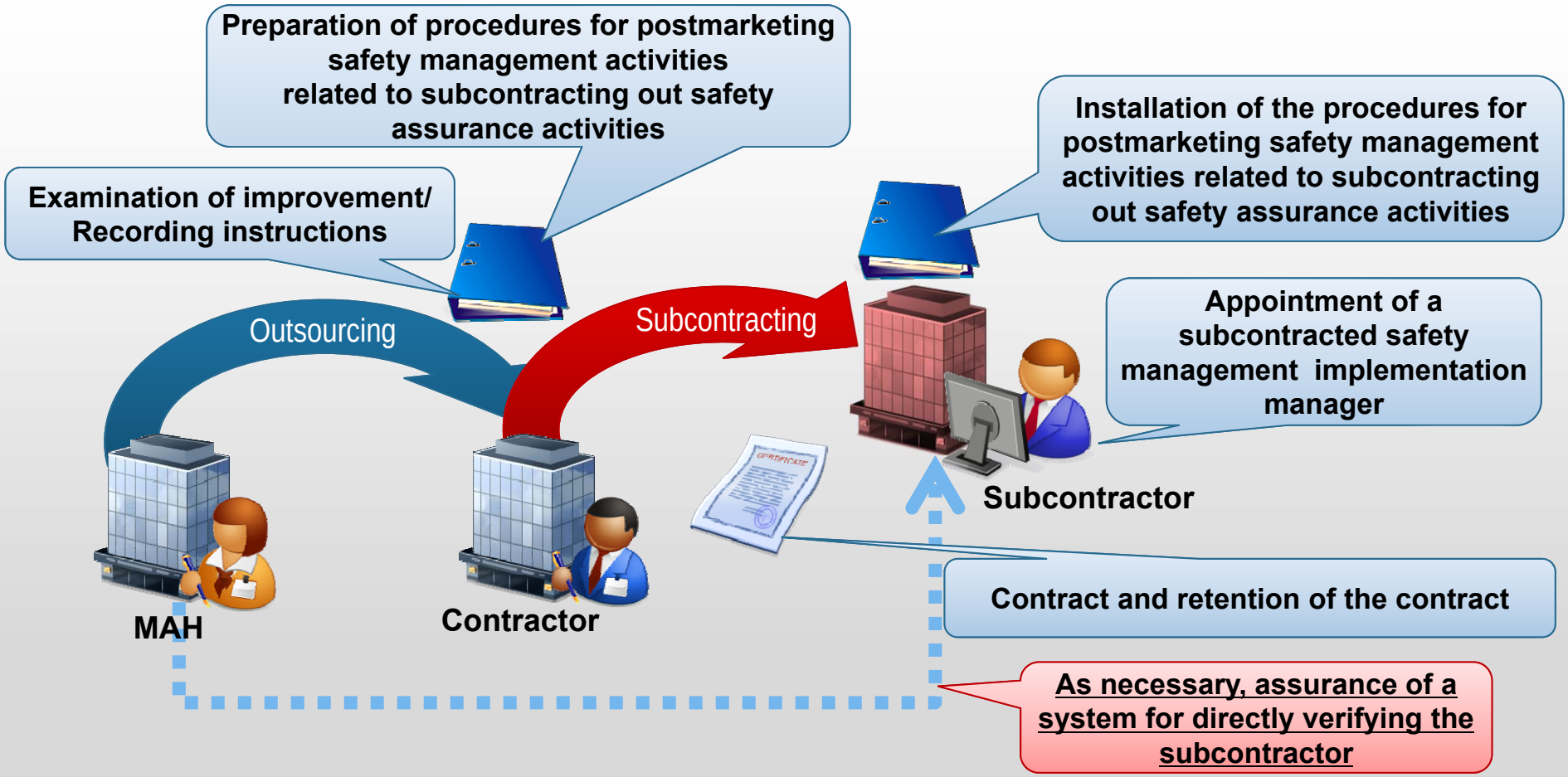


The same scope of activities for outsourcing may be subcontracted out.

*In either pattern, subcontracting out from the subcontractor is not permitted.

Subcontracting out of safety management activities (2)

- When subcontracting out, as with the outsourcing in the first stage, a manager shall be specified, procedures shall be prepared, and records shall be retained.



Other amended matters (1)

Addition of the purpose of the Act

In the purposes of the Act, “Prevention of the onset and spread of health and hygiene hazards associated with use” is specified as necessary regulations for pharmaceuticals. (Article 1 of the Act)

Addition of provisions of responsibilities

[Responsibilities of the government]

The government shall establish and implement necessary measures (Article 1-2 of the Act).

[Responsibilities of the prefectural governments]

The prefectural governments shall establish and implement measures according to the conditions of the regions while taking account of appropriate role allocation with the government (Article 1-3 of the Act).

[Responsibilities of pharmaceutical business **entities]**

Pharmaceutical business entities shall mutually exchange information and take other necessary measures to make efforts in ensuring the safety of pharmaceuticals and preventing the onset and spread of health and hygiene hazards associated with their use (Article 1-4 of the Act).

[Responsibilities of healthcare providers]

Healthcare providers shall make an effort in providing accurate and appropriate information on matters concerning proper use (Article 1-5 of the Act).

[Role of Japanese people]

Japanese people shall properly use pharmaceuticals and make an effort in increasing knowledge and understanding of their efficacy and safety (Article 1-6 of the Act).

Other amended matters (2)

Centralization of an organization to which reports from medical institutions should be sent

- **Where to make reports of adverse reactions etc. from medical institutions will be unified with that from MAHs and defined as the PMDA (in relation to Article 68-12 and 68-13 of the New Act).**

Use of information on relief benefit applications for safety measures

- **In order to use information for requesting adverse reaction and infection relief benefits provided by the PMDA for safety measures for pharmaceuticals, it is to be organized and investigated by the PMDA (in relation to Article 68-10-3 of the New Act).**