Package insert notification system

PMDA/MHLW
Contents

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- Malfunction reports of combination products
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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)

(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)

<table>
<thead>
<tr>
<th></th>
<th>Applicable products</th>
<th>Non-applicable products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
<td>• Ethical drugs (pharmacy drugs)</td>
<td>Over-the-counter drugs</td>
</tr>
<tr>
<td></td>
<td>• However, excluding the following:</td>
<td>Exceptional products listed in the left column</td>
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<tr>
<td></td>
<td>• <em>In vitro</em> diagnostics</td>
<td></td>
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<td></td>
<td>• Drugs not requiring approval</td>
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<td></td>
<td>• Pharmacy-compounded drugs</td>
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<td></td>
<td>• Guidance-mandatory drugs</td>
<td></td>
</tr>
<tr>
<td><strong>Medical devices</strong></td>
<td>Class IV medical devices</td>
<td>Classes I to III medical devices</td>
</tr>
<tr>
<td><strong>Regenerative medical products</strong></td>
<td>All products</td>
<td></td>
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</tbody>
</table>

* 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).

<table>
<thead>
<tr>
<th>1</th>
<th>Date of preparation or revision</th>
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<tbody>
<tr>
<td>2</td>
<td>Japan Standard Commodity Classification Number</td>
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<tr>
<td>3</td>
<td>Therapeutic category</td>
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<tr>
<td>4</td>
<td>Regulatory classification</td>
</tr>
<tr>
<td>5</td>
<td>Name</td>
</tr>
<tr>
<td>6</td>
<td><strong>Warnings</strong></td>
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<tr>
<td>7</td>
<td><strong>Contraindications</strong></td>
</tr>
<tr>
<td>8</td>
<td>Description</td>
</tr>
<tr>
<td>9</td>
<td>Indications</td>
</tr>
<tr>
<td>10</td>
<td>Dosage and administration</td>
</tr>
<tr>
<td>11</td>
<td><strong>Precautions</strong></td>
</tr>
<tr>
<td></td>
<td>- Precautions related to the indications</td>
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<td></td>
<td>- Precautions related to the dosage and administration</td>
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<td></td>
<td>- Careful administration</td>
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<tr>
<td></td>
<td>- Important precautions</td>
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<tr>
<td></td>
<td>- Drug interactions</td>
</tr>
<tr>
<td></td>
<td>- Adverse reactions</td>
</tr>
<tr>
<td>12</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>13</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>14</td>
<td>Pharmacology</td>
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<tr>
<td>15</td>
<td>Physicochemistry</td>
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<tr>
<td>16</td>
<td><strong>Precautions for handling</strong></td>
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<tr>
<td>17</td>
<td>Conditions for approval</td>
</tr>
<tr>
<td>18</td>
<td>Packaging</td>
</tr>
<tr>
<td>19</td>
<td>References and request for literature should be made to:</td>
</tr>
<tr>
<td>20</td>
<td>Name and address of manufacturer or importer</td>
</tr>
</tbody>
</table>

- **Geriatric use**
- **Use during pregnancy, delivery or lactation**
- **Pediatric use**
- **Effects on laboratory tests**
- **Overdosage**
- **Precautions concerning use**
- **Other precautions**

This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.
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 presented on the website of the PMDA.
  (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.

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.
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.

### Ethical drugs
- **Notification by paper media**
  - 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.

### Medical devices
- **Notification via the Internet**
  - Notification via the Internet
  - Confirmation/reception by staff
  - Publication on the day designated by a company

### Guidance-mandatory drugs
- **Procedure for presentation via the Internet**

### Regenerative medicinal products
- **Notification by paper media**

- **Publication**
  - Server
  - PMDA
  - Confirmation/reception by staff
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:

- Approval Number
- Therapeutic category
- Conditions for approval
- Name and address of the MAHs, etc.

- Dosage and administration
- Information specified by the JP and other standards

- Warnings/ Contraindications
- Precautions
- Precautions for handling

- All information presented in the package insert

- Package insert and other information (Information required to be presented pursuant to Article 52 of the Act.)

→ Obligation for documentation based on evidence obtained from the latest literature and other sources

- Information required to be notified (Notification is required when revised.)

→ Obligation for notification
Exception for existing products when revising package inserts

- 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:

**Information provision through DM and MRs, etc.**

- The former package inserts may be attached to products that have been marketed (distributed) at the time of revision.
- The former package inserts may be attached to the following products to be marketed after revision as long as certain conditions are satisfied:
  1. Those which will be marketed within 6 months* after revision at the latest;
  2. A new package insert is presented on the PMDA's website; and
  3. MAHs should promptly provide revised information to physicians, etc.

**Drug manufacturing/packaging**

- New package inserts shall be attached to products that will be marketed after 6 months** from revision (The former package inserts may not be attached.)

* Only when using materials printed before the revision of the Act

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

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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.

<table>
<thead>
<tr>
<th>Malfunctions of the device part present (including the case where there are health injuries suspected to be attributable to the device part)</th>
<th>Adverse reactions etc. associated with drugs present</th>
<th>Adverse reactions etc. associated with drugs not present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malfunctions of the device part not present</td>
<td>Reporting of adverse reactions only</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- 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)

Pattern 1: Outsourcing safety management activities to a contracted distributor

- MAH
- MAH (distributor)
- Subcontractor (e.g., analysis company)

Outsourcing

Subcontracting

Distribution via another MAH

- Collection of safety management information
- Analysis of safety management information
- Implementation of safety assurance measures

The above items may only be subcontracted out.

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

- Subcontractor (e.g., analysis company)
- Medical device MAH
- MAH

Outsourcing

Subcontracting

Supply of components

Combination product

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.

Preparation of procedures for postmarketing safety management activities related to subcontracting out safety assurance activities

Installation of the procedures for postmarketing safety management activities related to subcontracting out safety assurance activities

Examination of improvement/Recording instructions

Appointment of a subcontracted safety management implementation manager

Contract and retention of the contract

As necessary, assurance of a system for directly verifying the subcontractor

Outsourcing

Subcontracting

MAH

Contractor

Subcontractor
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).