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Administrative Notice

November 25, 2014

Safety Division, Pharmaceutical and Food Safety Bureau,  
Ministry of Health, Labour and Welfare

To: The committee on safety of medicines  
The Federation of Pharmaceutical Manufacturers' Associations of  
Japan

Notice concerning Revisions to the  
“Standard Workflow for the Revision of Drug Product Package Inserts”

This notification serves to inform you that the previous Administrative Notice, “Standard Workflow for the Revision of Drug Product Package Inserts”, dated February 10, 2010, has been revised as attached, in accordance with the subsequent Administrative Notices, “Provision of Drug Product Safety Information” (Notification No. 0715-3, by the Director of the Safety Division of the Pharmaceutical and Food Safety Bureau (PFSB), the Ministry of Health, Labour and Welfare (MHLW), dated July 15, 2011), “Points to Consider when Providing Notification, etc. concerning Package Insert Language” (Notification No. 0901-1, by the Director, Safety Division, PFSB, MHLW, dated September 1, 2014), and “Guideline on Revision of Precautions and Other Information” (Notification No. 0929-2, by the Director, Safety Division, PFSB, MHLW, dated September 29, 2014).

The revised Administrative Notice, “Standard Workflow for the Revision of Drug Product Package Inserts” is attached for your reference. This document will also be posted on the website of the Pharmaceuticals and Medical Devices Agency (PMDA), and is subject to further revision as necessary.



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**(Attachment)**

## **Standard Workflow for the Revision of Drug Product Package Inserts**

This document serves to provide an explanation of the standard workflow for the revision of drug product package inserts conducted by marketing authorization holders (hereinafter referred to as “MAH”), the Pharmaceuticals and Medical Devices Agency (PMDA), and the Safety Division of the Pharmaceutical and Food Safety Bureau (PFSB) of the Ministry of Health, Labour and Welfare (MHLW) (hereinafter called “MHLW”) for reference purposes. Please note that under exceptional circumstances (e.g., emergent issue), this workflow may be conducted differently from the protocols described herein.

### **I. Information collection and management activities by PMDA**

#### **1. Information collection**

- Information reported from MAHs in accordance with the “Act on Securing Quality, Efficacy, and Safety of Drugs, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, And Cosmetics” is collected into a database.
- PMDA also independently collects information related to drug safety from various sources, including the scientific literature.

#### **2. Information management**

##### **(1) Management of information by safety evaluation teams in PMDA’s Office of Safety II**

###### **(a) Evaluation of each Japanese adverse drug reaction (ADR) Report**

- As a general rule, the results of causality assessments, etc. pertaining to individual 15-day ADR reports (involving patient death or unknown serious ADRs) are entered into PMDA’s database during the next business day after the report is received. The safety evaluation teams subsequently conduct primary screening of the information contained in the database.
- The safety evaluation teams confirm the details of noteworthy 30-day ADR reports, including those concerning known serious ADRs, and then enter this information into the database. Primary screening of the information contained in the database is then conducted.
- A line listing of the ADR reports collected for a given week, including those



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concerning known serious 30-day ADRs, is created, and the primary screening of the database is then conducted based on this line listing.

- Based on the above information, each evaluation team will determine which ADRs, if any, reach the level of emergent issue<sup>1</sup>.

(b) Evaluation of infection reports, corrective action reports, and research reports

- Infection reports, corrective action reports, and research reports are reviewed by the evaluation teams and then judged as to which reports, if any, reach the level of emergent issue<sup>1</sup>. The results of these determinations are then entered into the database. Primary screening of the information contained in the database is then conducted.

(c) Evaluation of periodic infection reports

- Periodic infection reports are reviewed and then judged as to which reports, if any, reach the level of emergent issue<sup>1</sup>. The results of these determinations are then entered into the database. Primary screening of the information contained in the database is then conducted.

(d) Evaluation of information independently collected by PMDA

- All independently collected information is assessed to determine what, if any, information reaches the level of emergent issue<sup>1</sup>.

(2) Primary database screening (daily)

- With regard to the information organized in (1) above, the collection status of similar reports is also checked based on the database contents in order to search for signals (i.e., noteworthy ADRs).
- Signals are automatically detected from reports meeting certain conditions through the use of data mining techniques.

(3) Secondary screening

- (a) As a general rule, each safety evaluation team will hold weekly discussions concerning any signals detected in the primary screening in order to determine the necessity of making inquiries and/or holding in-person interviews with MAHs to proceed with assessments of the need for safety measures. Inquiries and/or in-person interviews with MAHs will be conducted in each of the following cases: an ADR is possibly related to some patients' deaths; many reports of an unknown serious ADR have been collected; or countermeasures have been taken in countries other than Japan with regard to the same ADR. In such cases, the safety evaluation teams

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<sup>1</sup> Emergent issue: If an ADR reaches the level of

emergent issue, the workflow will be skipped to 3 (3).



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should also consider the results of periodic reports concerning unknown, non-serious ADRs, periodic safety update reports, foreign ADR reports, and data mining reports.

- (b) The results of secondary screenings should be shared with the PFSB Safety Division at MHLW.

PMDA will request further information from MAHs as required at each stage of review.

## II. Situations necessitating implementation of safety measures

### 1. PMDA has determined that discussion of safety measures will be necessary

#### (1) Making inquiries to MAHs

- If potential safety measures are discussed at the secondary screening, PMDA will request an opinion statement from the applicable MAHs regarding whether the proposed safety measures are necessary (PMDA may also request an in-person interview with the MAH and provide instructions for document submission).
- As a general rule, MAHs must respond to inquiries from PMDA within one week after such inquiries are made. However, if an MAH cannot respond to PMDA within this period, that MAH must inform PMDA as to when the response will be provided.

#### (2) Review of safety measures

##### (a) When an in-person interview is conducted

- PMDA holds a discussion based on the response received from the MAH, and if PMDA determines that an in-person interview with the MAH is necessary, PMDA, as a general rule, will notify the MAH of such determination within one week after receipt of the MAH's response.
- MAHs must prepare the materials required pursuant to "Materials Required during Consultation" (see appendix) and submit them to PMDA by its pre-designated deadline.
- If PMDA determines that additional documents are required, PMDA will notify the MAH of such requirement and the applicable submission deadline.
- PMDA will review any findings including comments made by the MAH during the in-person interview, and will notify the MAH whether safety measures are necessary and the timeframe by which they should be implemented, whether an expert discussion is required, or whether any "revisions of precautions," will be necessary, in general either after the in-person meeting or within one week after submission of the materials required during consultation.
- PMDA will review any information, including comments made by the MAH



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during the in-person interview, and if PMDA determines that no safety measures will be necessary at that stage, the matter prompting the in-person interview will be classified as a noteworthy issue subject to primary screening.

(b) When an in-person interview is not conducted

- MAHs must prepare the materials required pursuant to “Materials Required during Consultation” (see appendix) and submit them to PMDA by its pre-designated deadline.
- If PMDA determines that additional documents are required, PMDA will notify the MAH of such requirement and the applicable submission deadline.
- PMDA will review any findings, including comments submitted by the MAH, and will notify the MAH whether safety measures are necessary and the timeframe by which they should be implemented, whether an expert discussion is required, or whether any “revisions of precautions,” will be necessary, within one week after submission of the required materials.
- PMDA will review any information obtained from the MAH, and if PMDA determines that no safety measures will be necessary at that stage, the matter will be classified as a noteworthy issue subject to primary screening.

(3) Publication of drug risk information for which assessment is ongoing

Of the risk information supported by a certain threshold of ADR reports or other safety information collected, risks under ongoing assessment that have been determined to meet the level of significance potentially leading to revision of package insert precaution information are published on the Medical Product Information section on PMDA website, to aid healthcare professionals’ efforts to maintain drug safety. Information concerning these risks is also provided to relevant academic organizations and other stakeholders as needed.

(4) Reviews and Expert Discussions

(a) If an Expert Discussion is not held

- As a general rule, PMDA notifies MAHs of the details of safety measures to be implemented (e.g. required revisions to the package insert) within two weeks after the required documents are prepared. If a package insert requires revisions, PMDA will issue to each applicable MAH a “consultation number” required for submission of a new package insert.
- MAHs must revise the package insert in accordance with the instructions provided by PMDA.



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(b) If an Expert Discussion is held

- PMDA generally conducts a review (within approximately 10-40 days) at the next Expert Discussion after the required documents have been prepared and received from the relevant MAHs (typically held every five weeks).
- When the required documents have been prepared and received from MAHs, PMDA will notify relevant MAHs that the matter in question will be discussed at the upcoming Expert Discussion.
- PMDA will immediately notify the relevant MAHs of the results of the Expert Discussion. (If there are many MAHs to be notified, PMDA will request the assistance of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ).)
- PMDA will notify MHLW, the relevant MAHs, and FPMAJ of the proposed measures in consideration of the Expert Discussions (including “consultation no.” issued if package insert revisions are necessary).

(5) Provision of notification of review results by PMDA

- As a general rule, PMDA will, within one week after the Expert Discussion, summarize the results of reviews conducted including proposed safety measures, and provide notification of such to MHLW.

(6) Implementation of regulatory action

- As a general rule, the PFSB Safety Division at MHLW will publish a notice concerning proposed safety measures on a Tuesday after approximately two weeks following the Expert Discussion (the third week).
- PMDA publishes the results of reviews conducted on the Medical Product Information section of its website.

\*PMDA will notify the relevant MAHs of the status of ongoing reviews as necessary should additional time be required for completion.

2. If an MAH requests consultation concerning safety measures

(1) Application for consultation

- If an MAH requests consultation concerning safety measures involving required revisions or amendments to a drug product package insert, such MAH must submit the appropriate application form by e-mail or facsimile to PMDA. When submitting such application, the MAH must also submit the materials required under “Materials Required during Consultation” (appendix).



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## (2) Setting the interview date

- As a general rule, PMDA will notify the MAH of its receipt of the application for consultation by e-mail or facsimile by the next business day. If an in-person interview with PMDA is to be held, the MAH will also be notified of any adjustments made to the interview schedule.

## (3) Preliminary review

- PMDA will review in advance the items to be addressed during consultation.

The provisions set forth in Section 1. (2) above (1. PMDA has determined that discussion of safety measures will be necessary; (2) Review of safety measures) shall apply hereinafter.

## 3. Others provisions

### (1) Class labeling

If class labeling<sup>2</sup> is determined to be necessary at any of the aforementioned stages, PMDA will notify the MAHs applicable to the class labeling and will hold an explanatory meeting with the assistance of the FPMAJ. Reviews and other activities related to the class labeling action should be performed in the same manner as the regular procedure.

### (2) Assessment of drug-drug interactions

As a general rule, affected MAHs must coordinate amongst themselves regarding how to react to the matter in question, and subsequently consult with PMDA. If the affected MAHs are unable to coordinate, if there are many affected MAHs, or if all affected MAHs are not known, the relevant MAHs may consult with PMDA.

### (3) Cases involving emergent issues

Cases involving emergent issues should be handled immediately. Accordingly, PMDA and MHLW will provide instructions to the relevant MAHs concerning revisions or amendments to package insert information regardless of the standard workflow procedures.

### (4) Consideration of corrective action, etc. in other countries

If, based on the relevant scientific literature and the like, any risk information that has garnered attention by foreign regulatory agencies or academic societies and that may also affect the products used in Japan is discovered, the PFSB Safety Division at MHLW and PMDA will also evaluate the safety concerns associated with such risk information, and will provide, in accordance with the procedures set forth under Section II.1.(3) above, a

<sup>2</sup> Class labeling: Review of ADRs determined to be related to drugs with certain shared and similar

pharmacological effects as well as the package inserts of drugs containing active pharmaceutical ingredients belonging to the applicable class.



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summary of the results of such evaluation to healthcare professionals in Japan as needed.

End





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## Appendix

### **Materials Required during Consultation**

Standard materials required for consultations concerning “Revisions to Warnings and Precautions”, to be prepared as the basis for package insert revisions made.

(Example materials)

- Comparative table of new and old package insert contents
- Line listing of adverse drug reactions occurring in Japan and materials describing the status of data collection
  - Also, as necessary, a line listing of adverse drug reactions occurring outside of Japan and materials describing the status of data collection
- Revised sections of the company core data sheet (CDS)
  - Also, as necessary, documents indicating the rationale for revisions made to the CDS
- Package inserts from countries other than Japan
- Status of measures taken by regulatory agencies in other countries (in case any action was taken overseas regarding the CDS revisions)
- Materials from the relevant literature
- Statement or expression from the MAH providing assurance that all of the above information was considered completely and to the best of the MAH’s knowledge based on the information available at the time