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Administrative Notice
September 27, 2021

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

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

Notice concerning "Standard Workflow for Consideration of Safety Measures such as Revision of Electronic Drug Product Package Inserts"

The workflow for revising package inserts for drugs is described in the Notice concerning Revision to the "Standard Workflow for the Revision of Drug Product Package Inserts" (Administrative Notice dated November 25, 2014) (hereinafter referred to as "Old Administrative Notice"). This is to inform you that, based on the proposal presented in the "Research for effective and improved implementation of the Risk Management Plan system for pharmaceuticals" (Research Expenses of Japan Agency for Medical Research and Development (Research on Regulatory Science of Pharmaceuticals and Medical Devices, Research and Development Representative: Mamoru Narukawa)), it has been organized as shown in the attached "Standard Workflow for Consideration of Safety Measures such as Revision of Electronic Drug Product Package Inserts."

The attachment pertains to drugs (excluding in vitro diagnostics) as before, but it is applicable also to quasi-pharmaceutical products, cosmetics and cellular and tissue-based products in general.

With the issuance of this administrative notice, the Old Administrative Notice will be abolished.

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Attachment

Standard Workflow for Consideration of Safety Measures such as Revision of Electronic Drug Product Package Inserts

This document serves to provide an explanation of the standard workflow for the consideration of safety measures such as revision of an electronic package insert of a drug (hereinafter referred to as "electronic package insert") conducted by marketing authorization holders (hereinafter referred to as "MAHs"), the Pharmaceuticals and Medical Devices Agency (PMDA), and the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau of the Ministry of Health, Labour and Welfare (MHLW) (hereinafter referred to as "Pharmaceutical Safety Division") for reference purposes. For urgent matters, the PMDA and the Pharmaceutical Safety Division may instruct the revision of the electronic package insert, etc. not according to this standard workflow because they need to be handled promptly.

I. Information collection, signal management, risk classification, and consideration/implementation of safety measures by PMDA

1. Information collection

- Information reported from MAHs in accordance with the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products and Cosmetics[1], information on relief claims, and reports from patients are collected into the PMDA's database for adverse drug reactions, etc. reports.
- PMDA collects information related to drug safety from various sources, including the scientific literature, information from foreign regulatory authorities, and information obtained using medical information databases.

[1] Including reports based on the Immunization Act and Clinical Trials Act in addition to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products and Cosmetics

2. Signal detection

○ Evaluating information and primary screening

PMDA evaluates the following information, detects signals[2], and confirms the necessity of actions for detected signals as soon as possible.

[1] Case reports of adverse drug reactions in Japan
[2] Case reports of infection
[3] Foreign corrective action reports
[4] Research reports
[5] Periodic safety reports
[6] Periodic infection reports
[7] Information collected by PMDA

The results of assessment of reports in category [1] to [4] are entered into the PMDA's database for adverse drug reactions, etc. reports. As a general rule, the results of causality assessments, etc. of reports pertaining to 15-day adverse reactions reports (involving patient death or unknown serious adverse reactions) in category [1], in addition to category [2], are entered into the PMDA database for adverse drug reactions, etc. reports during the next working day after the report is received. For reports in category [1] from MAHs, index values of signals by data mining method are calculated. Information obtained using a medical information databases are also utilized for signal detection.

At each of the following stages, PMDA examines the necessity of responding to signals as soon as possible and the necessity of sharing them with the Pharmaceutical Safety Division.
For events not identified as signals, PMDA continues to monitor them at the signal detection stage.

[2] Information that arises from one or multiple sources (including observations and experiments), that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify.
Source: ICH E2C (R2) guideline "Periodic Benefit-Risk Evaluation Report (PBRER)"

3. Signal validation

○ Secondary screening

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 further analysis (signal evaluation) based on related information (safety profile of drugs including descriptions in electronic package inserts, accumulation status of related reports, index value of signals, status of foreign regulatory authorities, results of signal detection/signal enhancement using medical information databases, etc.).

If additional information is necessary for review at each stage of evaluation of information, PMDA will make inquiries to MAHs.

For signals for which further analysis is judged to be necessary, PMDA will proceed with evaluation as validated signals (for which signal evaluation is judged to be necessary).

PMDA will complete the investigation of signals for which further analysis is considered unnecessary and continue monitoring at the signal detection stage.

4. Signal evaluation

For a validated signal as a result of the secondary screening, PMDA will evaluate whether it is a new risk[3] as follows.

- PMDA will make inquiries to MAHs and seek their opinions on whether or not the risk is new and whether or not safety measures are necessary (submission of materials may be requested).
- MAHs will, in principle, respond to the inquiries from PMDA within 2 weeks after inquiries are made. If it is difficult to respond by the deadline, MAHs will inform PMDA about the scheduled date of submission.

[3] Potential for undesirable outcomes related to the quality, safety and efficacy of the medicinal product with any undesirable outcome to the health of the patient or to public health or to the environment.
- Potential for undesired outcomes. The risk concept does not include the severity of the outcome.
- The time interval at which the risk exists should be identified.
- The safety risk level is expressed as probability multiplied by severity.

(Cited from the research report of "Basic research to enhance the drug risk management plan system and improve its effectiveness" (from 2018 to 2020) under the Research on Regulatory Harmonization and Evaluation of Pharmaceuticals and Medical Devices of the Japan Agency for Medical Research and Development (AMED)

- PMDA will hold a discussion based on clinical and non-clinical data, the status of the same ingredients/similar drugs, literature information, the status of foreign regulatory authorities, and the opinions submitted by MAHs, etc. In addition, PMDA will conduct a review based on the results of verification by epidemiological methods using medical information databases, etc. where necessary.
- If PMDA determines that additional documents are required, PMDA will notify the MAH of such a requirement and the applicable submission deadline.

If the review takes time, PMDA will notify the MAH of the review status within 2 weeks, in principle, after the submission of documents from the MAH.

If PMDA judges that it is not possible to draw a conclusion as to whether or not a signal is a new risk or a change in the risk classification is necessary because of insufficient evidence, or that a signal is not a new risk or no change in the risk classification is necessary, PMDA will communicate the review results to the MAH, and then terminate the review process and continue monitoring at the signal detection stage.

5. Consideration of safety measures based on risk classification

(1) Risk classification and consideration of safety measures

- For events determined to be risks by signal evaluation, PMDA will determine the significance of the risk and whether it is an identified risk or a potential risk.
- If safety measures including revision of the Risk Management Plan[4] (RMP), revision of electronic package insert for risk mitigation, provision of information to healthcare professionals) are considered necessary as a result of the risk classification described above, PMDA will consider the necessity of expert discussion, contents of the draft safety measures (whether or not issuance of instructions for "Revision of Precautions" is necessary), and when to implement these measures. The results will be communicated to the MAH within 2 weeks, in principle, after all materials necessary for the above decision are made available.
- If an expert discussion is not held, as a general rule, PMDA notifies MAHs of the review results (required revisions to the electronic package insert, etc.) within two

[4] Refer to the Risk Management Plan Guidance (PFSB/ELD Notification No0411-1, PFSB/ELD Notification No. 0411-2, April 11, 2012 https://www.pmda.go.jp/files/000153333.pdf)

weeks after the required documents are submitted.

(2) Disclosure of information on risks under evaluation

- If important risk information is suggested in a certain amount of accumulated case reports of adverse drug reaction, etc., for which the relationship with drugs is under evaluation and attention is being paid by MHLW and PMDA as it may lead to revision of precautions, etc., PMDA will publish it as the information on risks, etc. under evaluation for a certain period of time on the PMDA website (until the date of notification issuance if the information leads to issuance of notification instructing "Revision of Precautions"; otherwise, approximately 5 weeks after the posting of the survey results) so that healthcare professionals can ensure the safety. In addition, information will be provided to related academic societies, etc. where necessary.
- Before the disclosure of information on risks, etc. under evaluation, PMDA will share such information with the Pharmaceutical Safety Division.

6. Expert Discussion

(1) Implementation of Expert Discussion

- PMDA will deliberate the appropriateness of PMDA's judgment on the safety measures based on the signal evaluation results and risk classification at the Expert Discussion.
- In general, the deliberation will be made within approximately 10-40 days at the next Expert Discussion (typically held every five weeks) after the required documents have been submitted by the relevant MAHs.
- When the required documents have been submitted by MAHs, PMDA will notify relevant MAHs that the matter in concern will be discussed at the next Expert Discussion.

(2) Sharing of Expert Discussion results with relevant parties

- PMDA will immediately communicate the Expert Discussion results to the MAH (if there are many MAHs to be contacted, the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) will be requested to cooperate).
- PMDA will share the Expert Discussion results with the Pharmaceutical Safety Division.

If it is determined that no safety measures are required for a risk or that it is not a risk as a result of the Expert Discussion, PMDA will terminate the review process and continue monitoring at the signal detection stage.

7. Implementation of safety measures

If PMDA judges that safety measures are necessary as a result of the Expert Discussion, safety measures will be implemented. In principle, the revision of the electronic package insert shall be as follows.

(1) Communication of draft safety measures

- PMDA will notify the MAH of the "consultation reference number" necessary for notification of the package insert.
- PMDA will communicate the draft safety measures (including "consultation reference number") to the Pharmaceutical Safety Division, MAHs, and the FPMAJ when the notification instructing "Revision of Precautions" is issued.

(2) Issuance of notification of survey results from PMDA

- In principle, PMDA will summarize the survey results including the proposed safety measures within 1 week after the completion of the Expert Discussion (after finalization of the survey results based on the Expert Discussion) and notify the Minister of Health, Labour and Welfare.

(3) Implementation of safety measures

- In principle, the Pharmaceutical Safety Division will issue a notification instructing "Revision of Precautions" within approximately 2 weeks after receiving the notification of survey results from PMDA.
- On the same day as above, PMDA will publish the survey results on the PMDA website.
- The MAH will revise the electronic package insert to reflect safety measures.

If PMDA does not hold an Expert Discussion, safety measures are taken as necessary. The revision of the electronic package insert shall be as follows.

(1) Communication of draft safety measures

- PMDA will notify the MAH of the "consultation reference number" necessary for notification of the electronic package insert.

(2) Implementation of safety measures

- The MAH will revise the electronic package insert to reflect safety measures.

II. 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 electronic package insert, the MAH must submit the "Consultation Application Form (Revision of package inserts of drugs [excluding in vitro diagnostics], etc.)" by e-mail or facsimile to PMDA. When submitting such an application, in principle, the MAH must also prepare and submit the materials described in “Materials Required during Consultation for MAH” (appendix). If there is no material 1 to 9 described in the appendix to be submitted, that should be explained.

(2) Receipt

- 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 working day.

(3) Consideration of safety measures

- PMDA will review the contents of the consultation.
- The provisions set forth in "Section I. Information collection, signal management, risk classification, and consideration/implementation of safety measures by PMDA 4. Signal evaluation" shall apply hereinafter.

III. Other provisions

(1) Class labeling[5]

If class labeling is determined to be necessary, PMDA may notify the MAHs applicable to the class labeling and will hold an explanatory meeting with the assistance of the FPMAJ as needed.

(2) Assessment of drug-drug interactions

As a general rule, affected MAHs must coordinate amongst themselves regarding how to react to the matter in concern, and subsequently consult with PMDA. If the

[5] Review of risks considered 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.

affected MAHs are unable to be coordinated, there are many affected MAHs, or all affected MAHs are not known, the relevant MAHs may consult with PMDA.

(3) Consideration of corrective actions, etc. in other countries

If, based on the relevant scientific literature and the like, MHLW and the PMDA have started evaluation of any risk information that has gathered attention by foreign regulatory agencies or academic societies and that may also affect the products used in Japan, PMDA will provide a summary of the results of such an evaluation to healthcare professionals in Japan on its website as needed, in accordance with the procedures set forth under "Section I. Information collection, signal management, risk classification, and review/implementation of safety measures by PMDA, 5. Signal evaluation (2) Disclosure of risk information during evaluation, etc."

End

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(Appendix)　Materials Required for MAHs for Consultation

1. Comparative table of new and old package insert contents
2. Line listing of adverse drug reactions occurring in Japan and materials describing the status of data collection
3. Also, as necessary, a line listing of adverse drug reactions occurring outside of Japan and materials describing the status of data collection
4. Revised company core data sheet (CCDS) and revised sections
5. Documents indicating the rationale for revisions made to the CCDS
6. Package inserts in other countries and status of descriptions
7. Status of measures taken by regulatory agencies in other countries and status of consultation with regulatory agencies in other countries
8. Relevant literature
9. Opinions by the MAH based on all of the above information and specific reasons for considering that revision is necessary in Japan
10. Others