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PSEHB/ELD Notification No. 1205-1
PSEHB/SD Notification No. 1205-1
December 5, 2017

To: Commissioners of Prefectural Health Departments (Bureaus)

Director of Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
(Official seal omitted)

Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
(Official seal omitted)

Partial amendment of “Risk Management Plan templates and instructions”

The "Ministerial Ordinance to Partially Amend the Ministerial Ordinance on Standards for Conducting Post-Marketing Surveillance and Studies on Drugs" (Ordinance of the Ministry of Health, Labour and Welfare No. 116 in 2017) will be promulgated and enacted on April 1, 2018. Based on this Ministerial Ordinance, regarding the "Ministerial Ordinance on Standards for Conducting Post-Marketing Surveillance and Studies on Drugs" (Ordinance of the Ministry of Health, Labour and Welfare No. 171 in 2004, hereinafter referred to as "GPSP Ministerial Ordinance"), the “post-marketing database surveillance” will be newly defined as surveillance using a medical information database. Given that, “Risk Management Plan (hereinafter referred to as RMP) templates and instructions” (joint PFSB/ELD Notification No. 0426-2 and PFSB/SD Notification No. 0426-1 dated April 26, 2012 by the Director of Evaluation and Licensing Division and the Director of Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, hereinafter referred to as

"notification of RMP templates and instructions") is amended as described below. Please inform related companies and organizations under your jurisdiction of this notification. Handling of generic drugs is as shown in "Application of the Risk Management Plan Guideline for Generic Drugs" (joint PFSB/ELD Notification No. 0826-3 and PFSB/SD Notification No. 0826-1 by the Director of the Evaluation and Licensing Division and the Director of the Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated August 26, 2014).

Note

1 Partial amendment of the notification of RMP Templates and Instructions

(1) The description of the notification of RMP Templates and Instructions will be amended as shown in Attachment 1 "Old/new comparison table" of this notification.

(2) Of attached forms in the notification of RMP Templates and Instructions, "7. References" will be amended to "7. Attached documents."

(3) The procedure for description of the notification of RMP Templates and Instructions will be amended as the new/old comparison table in Attachment 2 of this Notification.

(4) The Annex of the notification of RMP Templates and Instructions will be amended as Attachment 3 of this Notification.

2 Date of application

From today, based on the example of the revised GPSP Ministerial Ordinance, the applicant (the marketing authorization holder) can plan the Post-Marketing Surveillance and studies to be conducted on and after April 1, 2018, prepare or change the RMP, and submit it to the Pharmaceuticals and Medical Devices Agency.

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Attachment 1

Old/new comparison table of the description in the notification of RMP templates and instructions

Before amendment	After amendment*
1. Preparation for the document of Risk Management Plan (a) (Omitted) (b) A document of Risk Management Plan can be acceptable for an active ingredient in some drugs that are different indication, administration, forms and routes of administration, etc. (c) (Omitted)	1. Preparation for the RMP (1) (Omitted) (2) A document of RMP can be acceptable for an active ingredient in some drugs that have different indications, dosages and administrations, forms** and routes of administration, etc. (3) (Omitted)
2. Submission of a draft of Risk Management Plan at the time of application for approval (a) When a new drug application is filed, the applicants for marketing authorization shall file a draft of Post-Marketing Surveillance/Clinical study Plan based on the 3-1-1-(11) and the attachment 2-11 of the notification entitled “Points of preparation for the data to be attached for application form in the new drug application” (PFSB/ELD Notification No. 899 dated June 21, 2001 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare). However, when the applicants for marketing authorization submit approval applications on and after April 1, 2013, a draft of Risk	2. Submission of a draft of RMP at the time of application for marketing approval (1) When a new drug application is filed, the applicant for marketing authorization shall file a draft of Post-Marketing Surveillance and study Basic Plan based on 3-1-1-(11) and Attachment 2-11 of the notification entitled “Points of preparation for the data to be attached for application form in the new drug application” (PMSB/ELD Notification No. 899 dated June 21, 2001 by the Director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare). However, when the applicant for marketing authorization submits approval applications on and after April 1, 2013, a draft of RMP should be submitted instead of a draft of Post-

Management Plan should be submitted instead of a draft of Post-Marketing Surveillance/Clinical study Plan. In addition, after the notice day of this notification, the applicants for marketing authorization may submit a draft of Risk Management Plan as data to be attached to the new drug application instead of a draft of Post-Marketing Surveillance/Clinical study Plan.	Marketing Surveillance and study Basic Plan.
(b) In terms of biosimilars/follow-on biologics, the applicants for marketing authorization shall file specific methods and plans of post-marketing surveillance and risk management based on the annex 9. of "the Guidelines for ensuring the quality, safety and efficacy of biosimilars/follow-on biologics" (PFSB/ELD Notification No. 0304007 dated March 4, 2009 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare). However, when the applicants for marketing authorization for biosimilars/follow-on biologics submit approval applications on and after April 1, 2013, a draft of Risk Management Plan should be submitted instead of a draft of the specific methods and plans of post-marketing surveillance and risk management. In addition, after this notification, the applicants for marketing authorization may submit a draft of Risk Management Plan instead of the draft of the specific methods and	(2) In terms of biosimilars/follow-on biologics, the applicants for marketing authorization shall file specific methods and plans of post-marketing surveillance and risk management based on Annex 9. of "the Guidelines for ensuring the quality, safety and efficacy of biosimilars/follow-on biologics" (PFSB/ELD Notification No. 0304007 dated March 4, 2009 by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare). However, for biosimilars/follow-on biologics for which approval applications are to be submitted on and after April 1, 2013, a draft of RMP should be submitted instead of a draft of the specific methods and plans of post-marketing surveillance and risk management.

plans of the post-marketing surveillance and risk management.	
3. Submission of the document for Post-Marketing Surveillance /Clinical study Plan or Risk Management Plan	3. Submission of the RMP and the Post-Marketing Surveillance and study Implementation Plan
(a) i) In the case of products which a draft of Risk Management Plan is submitted by the MAHs due to above 2-a) at the time of new drug application, the fixed document of Risk management Plan with reference data should be submitted one month before the timing of planned product market launch as a general rule, instead of the Post-Marketing Surveillance/Clinical study Plan under the section 3 of the notification entitled “Basic plans including post-marketing surveillance and studies pertaining to the re-examination of new medicinal products” (PFSB/ELD Notification No. 1027007 dated October 27, 2005 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare).	(1) i) In the case of products for which a draft of RMP is submitted due to the above 2-(1) at the time of the new drug application, an RMP should be submitted with attachments one month before the timing of the planned product market launch as a general rule, instead of the Post-Marketing Surveillance and study Basic Plan under Section 3 of the notification entitled “Basic plans including post-marketing surveillance and studies pertaining to the re-examination of new medicinal products” (PFSB/ELD Notification No. 1027007 dated October 27, 2005 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare).
ii) In the case of products which a draft of Risk Management Plan is submitted by the MAHs due to above 2-b) at the time of new drug application, the fixed document of Risk management Plan with	ii) In the case of products for which a draft of RMP is submitted by the MAHs due to the above 2-(2) at the time of the application for approval, an RMP with attachments should be submitted

reference data should be submitted one month before the timing of planned product market launch as a general rule instead of the specific methods and plans of post-marketing surveillance and risk management	one month before the timing of the planned product market launch as a general rule instead of the specific methods and plans of post-marketing surveillance and risk management.
(b) Each individual Post-Marketing Surveillance/Clinical study Plan related to the additional pharmacovigilance activities should be described in items in the Annex. As a general rule, the submitter should file them one month before the timing of planned product market launch.	(2) The Post-Marketing Surveillance and study Implementation Plan should be described in items in the Annex. As a general rule, the Post-Marketing Surveillance and study Implementation Plan should be filed as an attachment of the RMP one month before the timing of the planned start of the surveillance or clinical studies.
(3)•(4) (Omitted)	(3)•(4) (Omitted)
4. (Omitted)	4. (Omitted)
5. Others (a) When the MAHs change Risk Management Plan including the case of above 4, except for the minor change, the Risk Management Plan should be submitted to the PMDA. In addition, the author should underline the changed parts and put down with the latest contents.	5. Others Including the case of the above 4, for a change in the RMP, except for a minor change, the most updated RMP should be submitted to PMDA. At the time of submission, an outline of the contents of the changes (name of the applicable items, an outline of the contents of the changes, the reason for the changes, etc.) should be described in the column of change history, and then the changed part shall be underlined, and also a series of documents specifying the details of the contents of the changes (old/new comparison tables including the contents before and after the changes, history of

	the amendments, etc.) shall be submitted as a reference.
(b) The MHLW will issue notification regarding the form of periodic reports based on the implementation of Risk Management Plan later.	(deleted)

* The new edition has been reviewed in English and does not necessarily match the previous edition.

** Because of the correction of the Chinese characters, there is no difference in the English text

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Attachment 2

Old/new comparison table of the guide for developing the RMP in the notification of RMP templates and instructions

Before amendment	After amendment
1. General matters ○ (Omitted) ○ A submitter may attach a separate sheet with describing of "the attached document" in the column if all of the statement cannot describe within each column. ○ (Omitted) ○ (Omitted) ○ If a submitter files a draft of Risk Management Plan other than a point of drug application, the draft of Post-Marketing Surveillance/Clinical study Plan and materials for additional phamacovigilance activities and additional risk minimization activities should be submitted at the time of submission.	1. General ○ (Omitted) (deleted) ○ (Omitted) ○ (Omitted) ○ If a submitter files a draft of RMP other than a point of drug application, a draft of Post-Marketing Surveillance and Study Implementation Plans for additional pharmacovigilance activities and surveillance and studies for efficacy, and a draft of materials for additional risk minimization activities should be submitted at the time of submission.
2. Summary of product ○ (Omitted) ○In the remarks column, the following should be stated: ● The status of re-examination period or after the period, and the information of generic drug, etc. ● The name of the person in charge, affiliation and telephone number, etc.	2. Summary of product ○ (Omitted) ○ In the remarks column, the following should be stated: ・ The distinction of generic drug, etc. ・ The name of the person in charge, affiliation and telephone number, etc. ・ The name of the product and the company name in the case of a joint

● The name of the product and the company name in the case of a joint development product. If a Risk Management Plan is submitted to the PMDA by joint names of the relevant parties for their products, description of a joint development product is not required.	development product. If an RMP is submitted to PMDA by joint names of the relevant parties for their products, a description of a joint development product is not required.
3. Summary of Risk Management Plan ○ (Omitted) ○ (Omitted) ○ If there are some concerns for efficacy, the author should increase the number of columns based on user need. If there is no statement to be included in the column, the author may put N/A in the space. ○ If Pharmacovigilance activities, implementation of plans on surveillance and studies for efficacy and risk minimization activities are based on condition for approval and instructions, etc., of the Pharmaceutical Affairs and Food Sanitation Council, the fact should be described.	3. Summary of the RMP ○ (Omitted) ○ (Omitted) ○ If there are some concerns for efficacy, the author should increase the number of columns based on user need. (deleted)
8. "Organizational structure for Risk Management Plan" ○ (Omitted) ○ For the organizational structure for safety management and the organizational structure for post-marketing surveillance /clinical study, the author should outline general matters concerning its business, and should attach some documents	8. "Organizational structure for the RMP" ○ (Omitted) ○ For the "organizational structure for safety management" and the "organizational structure for Post-Marketing Surveillance and studies," the author should outline general matters concerning its business, and should attach some documents as

including organization chart, etc., which show the cooperation system between the relevant departments and the implementation of Risk Management Plan. The placement of relevant departments in the whole corporate structure should be shown in the documents.	attachments including an organizational chart, etc., which show the cooperation system between the relevant departments and the implementation of the RMP. The placement of relevant departments in the whole corporate structure should be shown in the documents.
○ (Omitted)	○ (Omitted)
9. Background information ○ Make a list for the attached documents to the Risk Management Plan ○ As background information, the submitter should attach the outline of document (for the Pharmaceutical Affairs and Food Sanitation Council) attached with the application form at the time of the new drug application, the review report, the review result report for the Pharmaceutical Affairs and Food Sanitation Council and the draft version of package insert.	9. Other "Attached documents" ○ Make a list for the attached documents to the RMP. ○ As attachments, the following documents should be prepared as attached. i) The Post-Marketing Surveillance and study Implementation Plans for additional pharmacovigilance activities and surveillance and studies for efficacy ii) The materials, etc. for additional risk minimization activities

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Attachment 3

1. Drug use-results survey implementation plan (general drug use-results survey, specified drug use-results survey, drug use-results comparative survey)

(1) Purpose of the survey
(2) Concerns for safety, concerns for efficacy
(3) Survey implementation plan (draft)
   1) Number of subjects of the survey and rationale
   2) Scope of subjects of the survey
   3) Number of institutions for each clinical department scheduled for survey
   4) Method of the survey
   5) Survey period
   6) Items to be surveyed
   7) Items to be analyzed and methods
   8) Organizational structure for conducting the survey (If it is the same as it is in the RMP, this should be stated.)
   9) When a part of the duties related to the survey is outsourced, the name and address of the contractor and the scope of the duties outsourced
(4) Additional measures that may be taken based on the results of the survey and the decision criteria for the initiation
(5) A planned milestone date to evaluate the implementation status of the survey and the results obtained, or to report them to PMDA, and its rationale
(6) Other necessary matters

Attachments
   1) Implementation guideline (draft)
   2) Registration form (draft)
   3) Survey form (draft)

2. Post-marketing database surveillance implementation plan

(1) Purpose of the survey
(2) Concerns for safety, concerns for efficacy
(3) Survey implementation plan (draft)
    1) Outline of the medical information database to be used in the survey
    2) Number of subjects of the survey and rationale
    3) Scope of subjects of the survey
    4) Method of the survey
    5) Period for the survey (data period)
    6) Items to be surveyed
    7) Items to be analyzed and methods
    8) Organizational structure for conducting the survey (If it is the same as it is in the RMP, this should be stated.)
    9) When a part of the duties related to the survey is outsourced, the name and address of the contractor and the scope of the duties outsourced
(4) Additional measures that may be taken based on the results of the survey and the decision criteria for the initiation
(5) A planned milestone date to evaluate the implementation status of the survey and the results obtained, or to report them to PMDA, and its rationale
(6) Other necessary matters

Attachments

1) Documents explaining the certainty of survey results

3. Post-marketing clinical study protocol

(1) Purpose of the study
(2) Concerns for safety, concerns for efficacy
(3) Study protocol (draft)
   1) Name and address of the person who intends to sponsor a post-marketing clinical study
   2) When a part of the duties related to the studies is outsourced, the name and address of the contractor and the scope of the duties outsourced
   3) Name and address of the medical institution (number of institutions for each clinical department where the study is scheduled)
   4) Name and title of the prospective investigator of the post-marketing clinical study
   5) Summary of the study drug
   6) Method of the study
   7) Matters related to selection of subjects (subjects of the study)
   8) Number of study subjects and rationale
   9) Items to be investigated such as follow-up items and evaluation items
   10) Study period
   11) Items to be analyzed and methods
   12) Matters concerning access to source documents
   13) Matters related to retention of records (including data)
   14) Name and title of the physician who is commissioned to a coordinating investigator for a post-marketing clinical study, if applicable
   15) Names and titles of physicians constituting the committee, if a post-marketing clinical study is commissioned
   16) If the Efficacy and Safety Evaluation Committee is established, describe accordingly.
   17) The person who intends to sponsor a post-marketing clinical study shall, when the study drug is expected to have no effect on the subjects and when the study is expected to include subjects from whom it is difficult to obtain written informed consent in advance to participate in the study, describe as such and the following matters.

i) Explanation that the post-marketing clinical study must include subjects from whom it is expected to be difficult to obtain written informed consent in advance for participation in the study
ii) Explanation that the expected disadvantages to subjects in the post-marketing clinical study are the minimum necessary

18) When a post-marketing clinical study involves subjects from whom, or from whose legally acceptable representatives, it is expected to be difficult to obtain written informed consent in advance to participate in the study, the person who intends to sponsor the post-marketing clinical study shall describe such a fact and the following matters:
i) Explanation that the current treatment is not expected to be sufficiently effective for the candidate subject.
ii) Explanation that the use of the study drug has the sufficient potential to avoid a life-threatening risk of the candidate subject.
iii) The fact that the Efficacy and Safety Evaluation Committee has been established.

19) Organizational structure for conducting the study (If it is the same as it is in the RMP, this should be stated.)

(4) Additional measures that may be taken based on the study results and the decision criteria for the initiation

(5) A planned milestone date to evaluate the implementation status of the survey and the results obtained, or to report them to PMDA, and its rationale

(6) Other necessary matters

Attachments

1) Subject information sheet (draft) and consent form (draft)
2) Case report form (draft)