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April 26, 2012
(Partially amended by PFSB/ELD Notification No. 0304-1 and PFSB/SD Notification No. 0304-1 dated March 4, 2013 and PSEHB/ELD Notification No. 1205-1 and PSEHB/SD Notification No. 1205-1 dated December 5, 2017)

To: Commissioners of Prefectural Health Departments (Bureaus)

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

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

Risk Management Plan templates and instructions

In regard to “Risk Management Plan (hereinafter referred to as RMP),” the Ministry of Health, Labour and Welfare (hereinafter referred to as MHLW) previously issued notifications entitled “Risk Management Plan Guidance” joint PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2 dated April 11, 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 and provided its guidelines. This notification sets up the specific forms for RMP and the handling of the submission, etc., as described below. Please inform relevant companies and organizations under your jurisdiction of this notification.

1. Preparation for the RMP

(1) A document of RMP should be prepared using the appended form.
(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) A document of RMP can be acceptable for joint names as well, when multiple Marketing Authorization Holders (hereinafter referred to as MAHs) collaborate on their pharmacovigilance activities and risk minimization activities for their products. In this case, even though the information is different for the drugs, the information should be described in the same column on each form because the differences of each item would be clarified.

2. Submission of a draft of RMP at the time of application for marketing authorization

(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-Marketing Surveillance and Study Basic Plan.
(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.

3. Submission of the RMP and the Post-Marketing Surveillance and Study Implementation Plan

(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 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 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.

(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) Submission methods: A fixed document may be directly brought or mailed to Section No. 1 of the Office of Review Administration, Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”).

(4) An original and two copies of the fixed document should be submitted.

4. Submission of the RMP when new safety concerns have been identified in the post-marketing phase.

When new safety concerns have been identified in the post-marketing phase and the MAHs might want to develop or change the RMP, contact PMDA regarding the timing of submission and the content of the plan.

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.

[Appended form]

RMP

DD/MM/YY

To: The Chief Executive of Pharmaceuticals and Medical Devices Agency

Address: The location of principal office of a corporation
Name: Company name and representative of a corporation, stamp

I hereby submit an RMP as stated below.

Outline of the product			
Date of market authorization		Therapeutic category	
Re-examination period		Approval number	
International birth date			
Brand name			
Active ingredient			
Strengths and dosage form			
Dosage and administration			
Indication			
Conditions for approval			
Remarks			

Change history
Date of previous submission

Summary of the changed contents:
Reasons for change:

1. Summary of the RMP

1.1 Safety specifications

Important identified risks	
(Name of a safety specification)	
	The reasons why it is identified as an important identified risk:
	The contents of pharmacovigilance activities and the reasons why they are chosen:
	The contents of risk minimization activities and the reasons why they are chosen:
(Name of a safety specification)	
	The reasons why it is identified as an important identified risk:
	The contents of pharmacovigilance activities and the reasons why they are chosen:
	The contents of risk minimization activities and the reasons why they are chosen:
(Name of a safety specification)	
	The reasons why it is identified as an important identified risk:
	The contents of pharmacovigilance activities and the reasons why they are chosen:
	The contents of risk minimization activities and the reasons why they are chosen:
Important potential risks	
(Name of a safety specification)	
	The reasons why it is identified as an important potential risk:
	The contents of pharmacovigilance activities and the reasons why they are chosen:
	The contents of risk minimization activities and the reasons why they are chosen:
(Name of a safety specification)	
	The reasons why it is identified as an important potential risk:
	The contents of pharmacovigilance activities and the reasons why they are chosen:

	The contents of risk minimization activities and the reasons why they are chosen:
(Name of a safety specification)	
	The reasons why it is identified as an important potential risk:
	The contents of pharmacovigilance activities and the reasons why they are chosen:
	The contents of risk minimization activities and the reasons why they are chosen:
Important missing information	
(Name of a safety specification)	
	The reasons why it is identified as important missing information:
	The contents of pharmacovigilance activities and the reasons why they are chosen:
	The contents of risk minimization activities and the reasons why they are chosen:
(Name of a safety specification)	
	The reasons why it is identified as important missing information:
	The contents of pharmacovigilance activities and the reasons why they are chosen:
	The contents of risk minimization activities and the reasons why they are chosen:
(Name of a safety specification)	
	The reasons why it is identified as important missing information:
	The contents of pharmacovigilance activities and the reasons why they are chosen:
	The contents of risk minimization activities and the reasons why they are chosen:

1.2 Concerns for efficacy

(Name of a concern for efficacy)	
	The reasons why it is identified as a concern for efficacy:
	Name of the surveillance and/or the studies related to the efficacy
	Objective, summary of the contents, and method of the surveillance and/or the studies, and the reasons why the surveillance and/or the studies are chosen

2. Summary of the pharmacovigilance activities

Routine pharmacovigilance activities	
Summary of the routine pharmacovigilance activities:	
Additional pharmacovigilance activities	
Name of the pharmacovigilance activity	
Name of the pharmacovigilance activity	
Name of the pharmacovigilance activity	

3. Summary of the plans for surveillance and studies for efficacy

Name of surveillance or study for efficacy	
Name of surveillance or study for efficacy	
Name of surveillance or study for efficacy	

4. Summary of the risk minimization plan

Routine risk minimization activities	
Summary of the routine risk minimization activities:	
Additional risk minimization activities	
Name of the risk minimization activity	
Name of the risk minimization activity	
Name of the risk minimization activity	

5. Lists of the pharmacovigilance plan, surveillance and studies for efficacy, and the risk minimization plan

5.1 A list of the pharmacovigilance plans

Routine pharmacovigilance activities				
Additional pharmacovigilance activities				
Name of the additional pharmacovigilance activities	Milestones for the number of cases/ Target number of cases	Milestone date for evaluation of the activities	Implementation status	Due date for preparation of the report

5.2 A list of plans on surveillance and studies for efficacy

Name of the surveillance and studies	Milestones for the number of cases/ Target number of cases	Milestone date for evaluation of the activities	Implementation status	Due date for preparation of the report

5.3 A list of risk minimization plans

Routine risk minimization activities		
Additional risk minimization activities		
Name of risk minimization activities	Milestones for the number of cases/ Target number of cases	Implementation status

6. Organizational structure for the RMP

6.1 Responsible persons

Responsible persons	Affiliation	Name
Safety management supervisor		
Chief administrator of Post-Marketing Surveillance and Studies		

6.2 Organizational structure for safety management

6.3 Organizational structure for Post-Marketing Surveillance and Studies

7. Attached documents

Guide for developing the RMP

1. General
   - The text should be laid out for Japanese Industrial Standards A4 paper.
   - For every particular items in the plan, if there is no statement to be included in the column, the author may put N/A in the space.
   - If a submitter files a draft RMP as a part of applications for new drugs, biosimilars/follow on biologics, generics and partial changes, it is recommended that the document should be submitted along with outline of the draft of the implementation plan and the materials for risk minimization activities at the time.
   - 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 products
   - If a submitter files a draft of RMP as a part of a drug application, the submitter should leave the undecided items such as “approval date,” “approval number” and “conditions for approval,” etc., blank. For the items of “therapeutic category,” “dosage and administration” and “indication,” etc., the author should describe the same contents as the marketing application form and put “planned” on each item.
   - 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 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 the RMP
   - For the safety specification, if there are some important identified risks, important potential risks and important missing risks, the author should increase the number of columns based on user need.
   - For “The reasons why it is identified as an important identified risk,” “The reasons why it is identified as an important potential risk,” and “The reasons why it is identified as important missing information,” based on the information from non-clinical data, clinical data and the situation of post marketing stage, the author should provide concise descriptions by attaching related information and literatures and using citation from the documents, etc. If a submitter files a draft of the RMP as a drug application, it should be considered whether the items in the document are consistent with the related items in the Common Technical Document.
   - If there are some concerns for efficacy, the author should increase the number of columns based on user need.

4. Summary of pharmacovigilance plans
   - For additional pharmacovigilance activities, the relevant safety specification, objectives and reasons, etc., should be described. If there are some additional Pharmacovigilance activities, the author should increase the number of columns based on user need.
   - If there are additional pharmacovigilance activities, the implementation plans should be submitted as Post-marketing Surveillance and Study Implementation Plans.

5. Summary of plans on surveillance and studies for efficacy
   - For the surveillance and studies for efficacy, the relevant specifications related to efficacy, objective and reasons, etc., should be described. If there are some surveillance and studies for efficacy, the author should increase the number of columns based on user need.
   - If there are surveillance and studies for efficacy, the implementation plans should be submitted as Post-marketing Surveillance and Study Implementation Plans.

6. Summary of the risk minimization plan
   - For additional risk minimization activities, the relevant safety specifications, objectives and reasons should be described. If there are some additional risk minimization plans, the author should increase the number of columns based on user need.

7. Lists of the pharmacovigilance plan, plan of surveillance and studies for efficacy and risk minimization plan
   - For each, the author should prepare each plan not only in practice but also under planning.
   - In the column for status of implementation, the author should describe the status of implementation of each activity at the time of the update of the RMP.

8. Organizational structure for the RMP
   - For the responsible person, the author should describe the names of the safety management supervisor and chief administrator of Post-Marketing Surveillance and Studies and if she/he concurrently serves as both, the fact should be described.
   - 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 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.
   - In the section of 6.2 “Organizational structure for safety management,” the name of the author of the RMP should be described clearly.

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

Annex

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)