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

**Translated by Office of Safety I,
Pharmaceuticals and Medical Devices Agency**

PFSB/ELD Notification No. 0426-2
PFSB/SD Notification No. 0426-1
April 26, 2012
As partially revised by PFSB/ELD Notification No. 0304-1
and PFSB/SD Notification No. 0304-1 dated March 4

To: Directors of Prefectural Health Departments (Bureaus)

From: 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 for authors

In regard to Risk Management Plan, the Ministry of Health, Labour and Welfare (MHLW) previously issued notifications entitled “Risk Management Plan Guidance” PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2 dated April 11, 2012 issued jointly 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 templates for Risk Management Plan and the handling of the submission, etc, as described below. Please inform Marketing Authorization Holders (MAHs) under your jurisdiction of this notification.

1. Preparation for the document of Risk Management Plan

a) A document of Risk Management Plan should be prepared using attached template.

b) A document of Risk Management Plan can be acceptable for an active ingredient in some drugs that are different indication, administration, forms and route of administration, etc.

c) A document of Risk Management Plan can be acceptable for joint names as well, when multiple MAHs collaborate on their pharmacovigilance activities and risk minimization activities for their products. In this case, even though the information is different with drugs, the information should be described in each the same column on a template, because the difference of each item would be clarified.

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 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.

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 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

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).

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 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.

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.

c) Submission methods : a submitter may directly bring or mail the fixed document of the Risk Management Plan or the Post-Marketing Surveillance/Clinical study Plan to the Office of review administration, Pharmaceuticals and Medical Devices Agency.

d) A submitter should file an original and two copies of the fixed document of Risk Management Plan or Post-Marketing Surveillance/Clinical study Plan.

4. Submission of Risk Management Plan 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 Risk Management Plan, contact the Pharmaceuticals and Medical Devices Agency (PMDA) regarding the timing of submission and the content of the plan.

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.

b) The MHLW will issue notification regarding the form of periodic reports based on the implementation of Risk Management Plan later.

[Appended form]

Risk Management Plan

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, Signature

I hereby submit a Risk Management Plan 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			
Remark			

Change history
Date of previous submission
Summary of the changed contents：
Reason for change：

1. Summary of Risk Management Plan

1.1 Safety Specification

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 activity 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 activity 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 activity 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 riskminimization activity 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 activity and the reasons why they are chosen：
Important missing information	
(name of a safety specification)	

	The reasons why it is identified as an important missing information：
	The contents of pharmacovigilance activities and the reasons why they are chosen：
	The contents of risk minimization activity and the reasons why they are chosen：
(Name of a safety specification)	
	The reasons why it is identified as an important missing information：
	The contents of pharmacovigilance activities and the reasons why they are chosen：
	The contents of risk minimization activity and the reasons why they are chosen：
(Name of a safety specification)	
	The reasons why it is identified as an important missing information：
	The contents of pharmacovigilance activities and the reasons why they are chosen：
	The contents of risk minimization activity 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 the concern for efficacy :
	Name of the surveillance and/or studies related to the efficacy
	Objective, summary of the content and method of the surveillance and studies and the reasons why the surveillance and/or studies are chosen :

2. Summary of Pharmacovigilance plan

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 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 Risk minimization activities

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 pharmacovigilance plan, surveillance and studies for efficacy and risk minimization plan

5.1 A list of pharmacovigilance plan

Routine phamacovigilance activities				
Additional phamacovigilance activities				
Names of the additional phamacovigilance activities	Milestones for the number of cases/ Target number of cases	Milestones 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

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

5.3 A list of Risk minimization plan

Routine risk minimization activities		
Additional risk minimization activities		
Names of risk minimization activities	Milestones for evaluation of the activities	Implementation status

6. Organizational structure for Risk management plan

6.1 Responsible persons

Responsible persons	Affiliation	Name
Safety management supervisor		
Chief administrator of Post-Marketing Surveillance/Clinical study Plan, etc.		

6.2 Organizational structure for safety management

6.3 Organizational structure for Post-Marketing Surveillance/Clinical study Plan, etc.

7. Background information

Guide for developing Risk Management Plan

1. General
   - The text should be laid out for Japanese Industrial standards A4 paper.
   - A submitter may attach a separate sheet with describing as ”the attached document” in the column if all of the statement cannot describe within each column.
   - 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 of Risk Management Plan as 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 Post-Marketing Surveillance/Clinical study Plan and the draft of the materials of Risk minimization plan at the time.
   - 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.

2. Summary of products
   - If a submitter files a draft of Risk Management Plan as part of 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, indication, etc., the author should describe the same content as the marketing application form and put “planned” on each item
   - In the remarks column, the followings 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.
     - 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.

3. Summary of Risk Management Plan
   - 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 an 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 the submitter files the draft of the Risk Management Plan 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. 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.

4. Summary of Pharmacovigilance plans
   - For additional pharmacovigilance plans, 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, these plans should be submitted as Post-Marketing Surveillance/Clinical study Plan

5. Summary of plans on surveillance and studies for efficacy
   - For the surveillance and studies for efficacy, the relevant specification related on 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, these plans should be submitted as Post-Marketing Surveillance/Clinical study Plan.

6. Summary of Risk Minimization Plan
   - For additional risk minimization plan, the relevant safety specification, 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 phamacovigilance 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 on going.
- The column for the status of implementation, the author should describe the status of implementation of each activity at the time of the update of the Risk Management Plan.

8. Organizational structure for Risk Management Plan

- For responsible person, the author should describe the names of safety management supervisor and chief administrator of post-marketing surveillance /clinical study 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 /clinical study, the author should outline general matters concerning its business, and should attach some documents 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.
- In the section of 6.2 “Organizational structure for safety management”, the name of the author of Risk Management Plan should be described clearly.

9. Background information

- Make a list for the attached the 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.