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

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

PFSB/SD Notification No. 0411-1
PFSB/ELD Notification No. 0411-2
April 11, 2012

To: Directors of Prefectural Health Departments (Bureaus)

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

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

Risk Management Plan Guidance

To ensure the safety of drugs, it is important to consider the ways to manage the risk of drugs on a consistent basis from the development phase to the post-marketing phase. In particular, to support the planning of pharmacovigilance activities in the early post-marketing phase of new drugs, MHLW previously issued a notification entitled "Pharmacovigilance Planning" (PFSB/ELD Notification No. 0916001 and PFSB/SD Notification No. 0916001 dated September 16, 2005, 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). In addition to this Pharmacovigilance Plan, MHLW have now formulated Guidance for development of a "Risk Management Plan," including a risk minimization plan to reduce the risk of drugs, as shown in the Annex. Please inform marketing authorization holders (MAHs) under

your jurisdiction of this Notification.

This Guidance shall be applicable to new drugs and follow-on biologics for which approval applications are submitted on or after April 1, 2013. As for generic drugs, the timing of application of this Guideline shall be informed separately.

(Annex)

Risk Management Plan Guidance
Table of Contents

1. Introduction

1.1 Objective

According to "Pharmacovigilance Planning" (PFSB/ELD Notification No. 0916001 and PFSB/SD Notification No. 0916001 dated September 16, 2005, 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; hereinafter referred to as the "ICH E2E Guideline"), it is required that the plan for pharmacovigilance activities (Pharmacovigilance Plan) is developed at the time of approval review and in the post-marketing phase based on the Safety Specification into which "important identified risks," "important potential risks," and "important missing information" are consolidated , and this instruction has been followed.

This Guidance is intended to present a basic concept for development of the Risk Management Plan that contains a risk minimization plan to reduce the risk of drugs in addition to the Safety Specification and Pharmacovigilance Plan described in the ICH E2E Guideline.

The objective of this Guidance is to ensure safety of drugs in the post-marketing phase by implementing the guidance and taking necessary safety measures based on a benefit-risk evaluation performed throughout the development, approval review and post-marketing phases.

This Guidance should be used taking into consideration the characteristics of individual drugs and their categories, such as new drugs, follow-on biologics, and generic drugs.

1.2 Scope

This Guidance is applicable to ethical use drugs, including generic drugs and follow-on biologics.

Based on this Guidance, development of the risk management plan should be considered at the following milestones:

- At the time of submission of approval application for new drugs (the term "new drugs" means new drugs as defined in Article 14-4, paragraph (1), item (i) of the Pharmaceutical Affairs Law [Law No. 145, 1960; hereinafter referred to as "the Law"]; the same shall apply hereinafter) ;
- At the time of submission of approval application for follow-on biologics;

- At the time of submission of approval application for generic drug versions of the original drugs for which additional pharmacovigilance activities or additional risk minimization activities (hereinafter referred to as “additional actions”) are being performed;
- At the time when new concerns regarding safety have been identified in the post-marketing phase.

2. Risk Management Plan

2.1 Development of Risk Management Plan

In order to always promote proper use of drugs and maintain an appropriate risk-benefit balance, MAHs and applicants for marketing authorization should identify the Safety Specification of drugs as described in section 3, and develop a Pharmacovigilance Plan as described in section 4 and a Risk Minimization Plan as described in section 6 based on the identified Safety Specification. When necessary, they should also develop a plan for post-marketing survey/study on efficacy as described in section 5. The MAHs and applicants for marketing authorization should then prepare a Risk Management Plan by consolidating these plans.

2.2 Points to Consider in Development of Risk Management Plan

When developing a Risk Management Plan, the necessity of additional actions should be considered at the same time as routine pharmacovigilance practices and routine risk minimization practices depending on the Safety Specification. A clear description should be provided in the Risk Management Plan about whether these actions are taken or not, together with the reasons and the methods. Because the validity of the Risk Management Plan is to be assessed during the approval review processes, in order to reflect the contents of the assessment of the Risk Management Plan, this Plan should be prepared so that consistency with the contents of the review reports be included.

As points of consideration for the necessity of additional actions, the followings are examples of them:

- Estimated number of patients to be treated with the drug;
- Situation or status of the drug administration;
- Identified risk population;
- Seriousness of target disease, seriousness of complications, and background incidence rate;

- Degree of influence of adverse drug reactions (ADRs) on the benefit-risk balance or public health conditions;
- Severity, frequency, reversibility, and possibility of prevention of serious ADRs;
- Effects expected from implementing risk minimization activities;
- Development or marketing situations in overseas;
- Differences in safety profiles between Japan and overseas;
- Situations and results of survey/study performed in overseas;
- Safety measures taken in overseas.

It should be noted that, even for drugs for which additional actions have been judged unnecessary as a result of considering the Risk Management Plan based on the Safety Specification, routine pharmacovigilance practices (including collection and reporting of information regarding ADRs and infections) as stipulated in Article 77-4, paragraph (2) of the Law and routine risk minimization practices (including provision of information through package inserts etc.) must be appropriately performed.

2.3 Setting of Milestones in Risk Management Plan

When developing a Risk Management Plan, the milestones for evaluating the results or for reporting to the Pharmaceuticals and Medical Devices Agency (hereinafter referred to the "PMDA") should be established by individual pharmacovigilance activities and risk minimization activities and be described on an activity-by-activity basis in the Risk Management Plan.

Although the milestones are to be established individually for pharmacovigilance activities and risk minimization activities, this plan of milestones should be the one that makes the management of the progress of overall activities and the progress of individual items of the Safety Specifications possible; for example, when examining more than one item of the Safety Specification in one activity, a milestone for evaluation or reporting of each item of Safety Specification should be established so that the target of each item of the Safety Specification be achieved at an appropriate time point.

The points to consider when setting the milestones include, for example, the following:

- When will it become possible to detect the predetermined frequency of adverse events (AEs) with sufficient reliability?

- When will it become possible to evaluate risk factors that affect the onset of AEs with sufficient accuracy?
- When will it become possible to use the results of pharmacovigilance activities that are being performed or planned?
- When will it become possible to evaluate the clinical and health importance of the items of the Safety Specification that are the targets of risk minimization activities? (If the Safety Specification is critical, evaluation of the effects of risk minimization activities should be conducted earlier and more frequently.)

2.4 Review of Risk Management Plan

Even after the Risk Management Plan has been developed, it should be reviewed depending on the post-marketing situations, and the contents of the Risk Management Plan should be revised to maintain an appropriate benefit-risk balance of the drug.

The review of the Risk Management Plan should be performed depending on the situations of individual pharmacovigilance activities and risk minimizing activities included in the Plan. The examples of the timing of this review are listed below:

- When the content of the Safety Specification needs to be changed; for example, at the time when new safety concerns have been identified after marketing;
- At a predetermined milestone in the Risk Management Plan;
- At the time of periodic reporting based on regulations or as directed by the PMDA;
- At the time of re-examination application for new drugs.

3. Safety Specification

3.1 Identification of Safety Specification

The Safety Specification should be identified for individual drugs in view of the properties of the drugsuch as the active ingredient and dosage form, characteristics of target diseases andthe patient population to be administered the drug, etc..

It is required to identify the Safety Specification which comprises the summary of important identified risks, important potential risks, and important missing information among identified risks, potential risks, and missing information of the pertinent drug. These important identified risks, important potential risks, and

important missing information are critical in that they may affect the benefit-risk balance of the drug or may cause or increase public health hazards on grounds such as they may become serious if they occur in humans or frequently occur.

For identification of Safety Specification, reference should be made to the ICH E2E Guideline.

3.1.1 Important Identified Risks

These are defined as important AEs among AEs for which the association with the drug is shown based on sufficient evidence. Identified risks include, for example, the following:

- ADRs or infections (hereinafter referred to as "ADRs etc.") for which the association with the drug has been well established in non-clinical studies and confirmed by clinical data;
- ADRs etc. for which causal relationship with the drug has been shown by the difference with the control group in well-designed clinical studies or epidemiological studies;
- ADRs for which causal relationship is suggested by temporal relationship or biological rationality derived from many spontaneous reports in the post-marketing phase.

3.1.2 Important Potential Risks

These are defined as important AEs among AEs for which the association with the drug has been suspected due to some factors but not been sufficiently confirmed by clinical data etc.. Potential risks include, for example, the following:

- Events that have not been observed by clinical data etc. although there are findings of safety concerns of the drug in non-clinical data;
- AEs for which causal relationship with the drug is not sufficiently shown, although causal relationship is suspected by the difference with the control group in clinical trials or epidemiological studies;
- AEs that have been detected as a signal from spontaneous reports in the post-marketing phase and have unclear causal relationship with the drug;
- ADRs etc. which have not been observed in the drug but have been observed in drugs of the same class with the same indications;

- Events that have not been confirmed in the clinical data etc., although the onset of the AEs are predicted from the properties of the pharmacological effects of the drug.

3.1.3 Important Missing Information

These are defined as critical information in cases where sufficient information has not been obtained at the time of development of the Risk Management Plan, and thus information is missing for prediction of safety in the post-marketing phase of the drug. Missing information includes, for example, the following:

- Information that is necessary for evaluating the safety in a certain patient population excluded from the clinical study, because, for example, high frequency use of the drug in this patient population is anticipated in real-world practice setting.

3.2 Review of Safety Specification

MAHs should always review the Safety Specification of the drug according to the ICH E2E Guideline. When new safety concerns have emerged as a result of post-marketing pharmacovigilance activities etc., the contents of the Safety Specification should be immediately reviewed. When the Safety Specification is amended, necessary measures (e.g. review of the Risk Management Plan and revision of related documents including the Risk Management Plan) should be taken.

4. Pharmacovigilance Plan

The content of the Pharmacovigilance Plan should be considered based on the following, using the ICH E2E Guideline as a reference.

4.1 Routine Pharmacovigilance Practices

MAHs should summarize their routine pharmacovigilance practices and their implementation system.

4.2 Additional Pharmacovigilance Activities

The necessity, the reasons, methods, etc. of additional pharmacovigilance activities should be considered based on the Safety Specification and summarized with the

implementation system. For the methods of pharmacovigilance activities including pharmacoepidemiological methods utilizing a healthcare information database, reference should be made to the "Pharmacovigilance Methods" in the Annex of the ICH E2E Guideline. In addition, the following points should be considered:

- Because rare and serious ADRs of new drugs may be observed early in the post-marketing phase, it is important that MAHs ensure to provide medical institutions with correct information and alerts about it, and remind them to promote understanding of proper use, collect information of serious ADRs etc. quickly, take necessary safety measures, and minimize health hazards from the ADRs etc. Therefore, if necessary, Early Post-marketing Phase Vigilance is required as additional pharmacovigilance activities. As for Early Post-marketing Phase Vigilance, reference should be made to relevant laws, regulations, and notifications, such as "Ministerial Ordinance on Good Vigilance Practice (GVP) for drugs, quasi-drugs, cosmetics, and medical devices" (Ordinance of the Ministry of Health, Labour and Welfare No. 135, 2004) and "Implementation Methods for Early Post-marketing Phase Vigilance for Prescription Drugs" (PFSB/SD Notification No. 0324001 of the Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare; dated March 24, 2006).

- In the post-marketing phase, new safety concerns, such as serious or fatal ADR,may be identified by accumulated information from ADR reports pursuant to Article 77-4-2 of the Law, and thus the Safety Specification may need to be modified. If this happens and the MAHs have implemented additional risk minimization activities, they are also required to conduct additional pharmacovigilance activities to evaluate the effect of the risk minimization activities.

- If the incidence rates of AEs in a patient population to be treated with the drug are high, and if the background incident rates of the AEs in this population are also considered high because of the natural course of the primary disease or complications, it may be difficult to determine whether or not the AEs are ADRs of the drug. When this type of situation occurs, the need for conducting additional pharmacovigilance should be considered.

If MAHs are to plan and conduct additional pharmacovigilance activities based on the newly identified Safety Specification issues, they should preliminarily consult with the PMDA.

4.3 Implementation Plan for Additional Pharmacovigilance Activities

When additional pharmacovigilance activities are implemented, a Risk Management Plan should be prepared or revised. A summary including the following items regarding the individual pharmacovigilance activities should be briefly described in the Risk Management Plan. In addition, a detailed implementation plan for individual pharmacovigilance activities should be prepared.

- Title of the implementation plan;
- Safety Specification;
- Implementation plan for the pharmacovigilance activities of the drug (draft);
- Objective of the pharmacovigilance activities of the drug;
- Rationale for the implementation plan of the pharmacovigilance activities of the drug
- Possible additional actions to be taken based on the results of the pharmacovigilance activities of the drug and the decision criteria for initiating them;
- Milestones for evaluating the implementation status and the results of the pharmacovigilance activities of the drug or for reporting them to the PMDA, and the rationale for the milestones.

When more than one item of the Safety Specification is dealt with by a single pharmacovigilance activity, this should be described.

When post-marketing clinical trials are conducted, the details of monitoring regarding the Safety Specification and rules on discontinuation of the study should be described. When necessary, the milestones of providing information to the Efficacy and Safety Assessment Committee specified in Article 19 of the "Ministerial Ordinance on Good Clinical Practices" (Ordinance of the Ministry of Health and Welfare No. 28, 1997) and of interim analyses of the trial should be described in the Risk Management Plan.

When information regarding efficacy is collected through surveys, trials, or studies as part of pharmacovigilance activities, this should be described.

5. Plan for Survey/trials on Efficacy

When a survey/trial is conducted to collect efficacy information of the drug, a summary of the objective of and the methods for the survey/trial should be briefly described using section 4.3 as a reference. In addition, collection of efficacy information should be taken into consideration when developing the Pharmacovigilance Plan.

6. Risk Minimization Plan

The risk minimization plan refers to the consolidated individual risk minimization activities conducted to minimize the risk of the drug and to maintain a appropriate benefit-risk balance based on information obtained by the time of approval, information on safety and others collected through the post-marketing pharmacovigilance activities, and evaluation of the information. The risk minimization activities are classified into two categories; i.e., routine activities conducted for all drugs and additional activities conducted, if necessary, according to the characteristics of the product in addition to the routine risk minimization practices.

6.1 Routine Risk Minimization Practices

Routine risk minimization practices include preparing package inserts describing approved items such as “Dosage and Administration”“Indications” and “Precautions” as specified in Article 52 of the Law, revising them as necessary, and providing information of the contents to healthcare professionals. The contents of these practices together with the implementation system should be summarized as the routine risk minimization practices.

In addition, the Drug Guide for Patients prepared based on the “Guideline for Developing the Drug Guide for Patients” (PFSB Notification No. 06300001 of the Director-General of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour, and Welfare; dated June 30, 2005) and the “Use of the Drug Guide for Patients” (Joint PFSB/SD Notification No. 0228001and PFSB/CND Notification No. 0228002 issued jointly by the Director of Safety Division and the Director of Compliance and Narcotics Division, Pharmaceutical and Food Safety Division, Ministry of Health, Labour and Welfare; dated February 28, 2006) should be regarded as part of the routine risk minimizing practices.

6.2 Additional Risk Minimization Activities

Additional risk minimization activities include, for example, provision of information, especially on the Safety Specification, to healthcare professionals, provision of information to the patients to be treated with the drug, and establishment of conditions for the use of the drug as described below, in addition to routine provision of package insert information. The MAHs should consider the necessity of implementation of these risk minimization activities or combinations of them depending on the characteristics etc. of individual drugs, and develop an additional risk minimization plan.

6.2.1 Provision of Additional Information to Healthcare Professionals

- Provision of information based on Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance is conducted during the first six months from the time of initial marketing to promote understanding of the proper use of the drug and minimize the harm of ADRs etc. by collecting information on serious ADRs etc. and taking necessary safety measures. It is also part of the additional pharmacovigilance activities as described in section 4.2 as well as the additional risk minimization activities that ensure to provide information and alerts etc. to medical institutions.

- Preparation and provision of materials for proper use

Regarding the Safety Specification, MAHs should consult with the PMDA and prepare materials for the proper use of the drug and provide them to healthcare professionals to ensure that they are well aware of the proper use.

- Rapid release of information obtained by post-marketing pharmacovigilance activities

Regarding the Safety Specification, when particular caution should be exercised regarding the use of the drug, MAHs should release the accumulated information such as the ADRs etc. which was obtained through the post-marketing pharmacovigilance activities on the their websites which are not targeted to limited users, and update the information at an appropriate frequency to ensure that healthcare professionals are well aware of the information. The MAHs should also consider working together with academic associations etc. and also publishing the information on the PMDA website.

- Others

If available, MAHs may use guidelines etc. on the proper use of the drugs, prepared by third parties, such as academic associations relevant to Safety Specification issues.

6.2.2 Provision of Information to Patients

- Preparation and provision of materials according to the Safety Specification

Regarding the Safety Specification, MAHs should consult with the PMDA and prepare and provide materials for patients describing specific precautions etc., such as a patient handbook, depending on the characteristics of the drug.

6.2.3 Establishment of Conditions of the Use of the drug

MAHs should establish conditions of the use of the drug, as necessary, to ensure proper and safe use of the drug according to the properties of the drug or the nature of the disease. The MAHs should take appropriate measures in marketing the drug, such as distributing their products only to medical institutions that can meet the conditions of the use of the drugs. These conditions are established in the forms such as the description of Precautions in the package inserts of the drug, regulations as conditions for approval, and regulations as part of safety control procedures. The conditions of the use of the drug include, for example, the following:

- Securing of use by physicians with sufficient expertise and experience

If drugs with a narrow therapeutic range or possible serious ADRs are to be used, MAHs should require prescribing physicians to have sufficiently high expertise and experience on the treatment of the disease. As for drugs that require special precautions for use, MAHs should also set certain requirements to secure physicians' expertise and experience, such as participation in a training session regarding the use of the drug etc., and require the physicians to register to the MAHs' program before using the drug.

- Securing the management system of the use of the drug

As for drugs which may lead to fatal course associated with serious ADRs or require strict management of the conditions of patients after administration, MAHs should require healthcare professionals to secure the management system of the use of the

drug such as the use of the drug only in medical institutions where sufficient emergency treatment is available or under hospitalization. In addition, for drugs requiring special management, securing of a management system and registration of physicians, pharmacists, etc. should be required.

- Careful selection of treatment patients

For drugs that need careful selection of treatment patients to ensure efficacy and safety, MAHs should establish conditions by taking into consideration the conditions of patients, medical history, treatment history, concomitant drugs, etc. In cases where special caution needs to be exercised, pre-confirmation of the eligibility of the patients, monitoring, registration of the treatment patients to the MAHs' program, etc. are required.

- Informed consent prior to administration of the drug

Regarding drugs that have a high risk of onset of fatal ADRs and especially require the understanding of patients to facilitate early detection of those ADRs or to ensure communication systems with their physicians, conditions for administration of these drugs should be established in a way that sufficient explanation on the efficacy, safety, etc. of the drug are given to the patients and their families and consent from them are received prior to administration. In addition, to avoid specific serious risks, materials and educational programs for patients should be provided to assist the understanding of patients and their families and to ensure awareness of risks.

- Specific tests etc.

In order to select patients who are appropriate for the treatment or to prevent specific possible ADRs etc. with the use of the drug, MAHs should establish conditions that certain tests etc. be performed before or after the administration of the drug.

6.2.4 Other Activities

- Devising failsafe labeling, containers, packaging, etc.

Specific measures concerning labeling, containers, packaging, etc. may be taken to prevent human errors etc. from happening.

6.3 Implementation Plan for Additional Risk Minimization Activities

When implementing additional risk minimization activities, the Risk Management Plan should be prepared or revised. A summary of individual risk minimization activities being implemented or planned to be implemented including the following should be briefly described in the Risk Management Plan:

- Safety Specification;
- Objective of the risk minimization activities;
- Specific contents of the risk minimization activities;
- Rationale for implementing the risk minimization activities;
- Possible additional actions to be taken based on the results of the risk minimization activities of the drug and the decision criteria for initiating them;
- Milestones for evaluating the implementation status and results of the risk minimization activities of the drug or for reporting them to the PMDA, and the rationale for the milestones.

7. Evaluation of the Risk Management Plan and Report to the PMDA

The implementation status and the results of individual pharmacovigilance activities, surveys/trials on efficacy, and risk minimization activities should be evaluated appropriately at their respective milestones according to the Risk Management Plan. At the same time, the benefit-risk balance of the drug should also be evaluated and considered based on the information obtained from individual activities conducted according to the Risk Management Plan.

As for new drugs which are in the re-examination period, a summary of the contents of evaluation should be reported at the time of submitting periodic safety reports as specified in Article 63 of the Enforcement Regulations (Ordinance of the Ministry of Health and Welfare No.1, 1961) regarding reports stipulated in Article 14-4, paragraph (6) or in the first half of Article 14-5, paragraph (2) of the Law. As for other drugs, the timing of reporting should be described in the Risk Management Plan depending on the contents of the additional actions.

The review results of the Risk Management Plan should also be reported together with the above report. If there are changes in the plan, MAHs should preliminarily consult with the PMDA, as necessary. The PMDA checks the contents of the report, and if it considers that some measures should be taken, the PMDA will give directions to MAHs.