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Risk Management Plan (RMP) Guidance (Draft)

I. Introduction

1. Objective

- This guidance is intended to propose a standard concept for “Pharmacovigilance Plan” and “Risk Minimization Plan” by Marketing Authorization Holders (MAHs) in order to deal with “Important identified risks”, “ Important potential risks” and “Important missing information” as shown in Safety Specification in the time of approval review and during the period of post-marketing in accordance to”Pharmacovigilance Planning - ICH Harmonised Tripartite Guideline: Notice No. 0916001, from the Director of the Evaluation and Licensing Division and the Director of Safety Division Pharmaceutical and Food Safety Bureau, and Ministry of Health, Labour and Welfare (MHLW), dated September 16, 2005 (herein after E2E Guideline)
  The whole plan is called “Risk Management Plan (RMP).”

- This guidance should be used as a guideline when the MAH considers further surveillances and studies regarding the safety of the product and additional actions to mitigate risks in the time of approval review and the post-marketing phase.

- This guidance is intended to aid to improve safety measures based on the assured post-marketing safety, the benefit/risk assessment and the review of them.

2. Scope

- The products which are subject to "Risk Management Plan (RMP)" and the time when the Plan is applied are described below:

  - In the time of approval review of new drugs (include new additional indication and dosage, revised/additional dosage and administration, new combination drug, additional dosage form: the same shall apply hereinafter), and when Safety Specification is newly submitted during the re-examination period.

  - When Safety Specification is newly submitted in post-marketing phase of generic drugs and drugs for which the re-examination was completed.

  - At the time of approval of the generic, in the case that its reference drug has already obligated to develop an additional risk minimization activity.

- The predicate rule for submitting the "Basic plans of post-marketing surveillance (PMS)"will be revised to contain the RMP and the plan will include "Pharmacovigilance Plan" and "Risk Minimization Plan". In the plan, the MAH should also include an implementation plan of benefit/risk assessment.

II. Safety Specification

1 The MAH should present " Important identified risks", " Important potential risks" and " Important missing information" as Safety Specification in order to review whether additional actions are needed in Pharmacovigirance Plan and risk minimization activity for the appropriate benefit-risk balance with taking into account of the characteristics of the treatment population, disease and administration.

2 Safety Specification should be a summary of the following important potential risks which may affect the benefit/risk balance. As to preparing the Safety Specification, the MAH should refer to "E2E Guideline".

2-1."Important identified risks": severe or frequent adverse drug reactions (ADRs) (includes drug interaction):

  - ADRs which are fully verified in non-clinical studies as well as in clinical data.

  - ADRs which are suggested causal relationships to a drug by studies including clinical trials.

- ADRs which are strongly suggested causal relationships to a drug based on the ADR reports.

2-2.“Important potential risks”：adverse events (AEs) that are required further collecting information because of safety concerns such as cases (includes drug interaction).

- Severe and frequent AEs which occurred in clinical trials or other clinical use (the causal relationships unclear).
- Potential serious ADRs which occurred in clinical trials and other clinical use.
- AEs which are identified in non-clinical studies but not identified in clinical trials.
- AEs which are not identified in clinical studies but pharmacologically predictable.
- AEs which are identified in another drug of the same class but not identified in the drug.
- Accumulated the ADR reports with unclear causal relationship to the drug.

2-3. “Important missing information”: information which did not acquired at the time of submission of RMP and suggests that it has a limitation in the estimation of the drug safety in the post-marketing setting.

e.g.) The safety information essential for a certain patient population that is excluded from the clinical trials but need to be considered about the drug safety, due to high frequency of the drug use in a practical clinical setting.

3. The MAH must identify the safety issues as Safety Specification in the time of approval review and the post-marketing phase. The RMP which is included in the "Basic plans of PMS" should be developed by identifying Safety Specification as the starting point, as with described in E2E Guideline.

4. The Common Technical Document (CTD), especially the Overview of Safety [2.5.5], Benefits and Risks Conclusions [2.5.6], and the Summary of Clinical Safety [2.7.4] sections, includes information relating to the safety of the product, and should be the basis of the safety issues identified in the Safety Specification.

5. For Safety issues for which were not able to be identified at the time of application, the MAH should describe in RMP that the potential issues were pointed out in the review process (e.g., review reports or responses of inquiries as support of the application).

6. As a result of post-marketing pharmacovigilance, if the MAH needs to add an additional Safety Specification, the "Basic plans of PMS" relating to RMP should be revised. And the basis of the additional Safety Specification should also be included in the plan. The additional Safety Specification should be included in regular reports such as periodic safety reporting.

III. Risk Management Plan (RMP)

1. Based on the “Important identified risks”, “Important potential risks” and “Important missing information” which are identified as Safety Specifications, the MAH should develop the “Pharmacovigilance Plan” and “Risk Minimization Plan”, the whole plan should be submitted as RMP.

2. RMP should be reviewed for consistency with its review report. Depending on the Safety Specification, the MAH should clarify whether an additional action should be implemented besides the regular pharmacovigirance plan and risk minimization activity. And the MAHs should also clarify the reason of that.

3. Even if it is not considered that the drug needs to be taken an additional action in safety specifications, the MAH is required to submit Adverse Drug Reaction (ADR) under the provision of Article 77 4-2 of the Phramaceutical Affairs Law. In principle, Early Post-marketing Phase Vigilance (EPPV) is required to be conducted for all new drugs.

4. Even if it is not considered that the drug needs an additional action in safety specifications, information provision by the package insert is required as routine risk minimization activity. The MAH also should provide information based on the EPPV using additional materials for new drugs.

5. If it is considered that the drug needs additional pharmacovigilance and that use-cases surveillance including specified use-cases surveillance should be implemented, the MAH should clarify the objectives of the survey and pays attention to implement the RMP in an appropriate manner.

6. The MAH also should make a point to utilize methods of pharmacoepidemiology as use-cases surveillance.

7. In the "Pharmacovigilance Plan" and "Risk Minimization Plan", when the MAH reviews the need of additional actions, the following should be considered.

    7-1. The impact of ADRs, the severity, frequency, reversibility and preventability on severe ADRs

7-2. The severity of disease included in drug indications, the severity and the background incidence rate of complications

7-3. Estimated number of patient exposure

7-4. Identified risk populations

7-5. Expected benefits by conducting risk minimization activity

7-6. Treatment duration

7-7. World-wide market authorization status

7-8. Results of overseas surveillance and studies (if it is changed, the points which should be taken into account)

7-9. The difference in safety profiles between Japan and overseas

7-10. Safety measures which was taken in overseas

If an additional action is required in pharmacovigilance plan and/or risk minimization activity, the MAH should clarify the reason and the method of the action. In the case that it is not considered the drug needs an additional action, the MAH should clarify the reason.

IV. Pharmacovigilance Plan

1. Usual Pharmacovigilance Plan

For usual Pharmacovigilance Plan, each MAH should sum up succinctly routine pharmacovigilance practices and implementation system.

2. Consideration and summary of Additional Pharmacovigilance Plan

2-1. The MAH should describe the summary of the necessity of additional Pharmacovigilance Plan and the reason for that, and a method of Pharmacovigilance Plan in a succinct manner. When the MAH considers a method of additional actions, the MAH should choose a method with considering how to utilize it and what kind of result you can expect. In addition, for the method of Pharmacovigilance Plan, the MAH should refer to the ANNEX of “E2E Guideline” as well as take into account the possibility of phramacoepidemiology studies which utilize medical information databases.

Additional Pharmacovigilance Plan for Safety Specification（examples of description）

Safety Specification	Reason why an additional action is required (examples)	Methods of Pharmacovigilance (examples)
Important identified risks	- Severe ADRs which may lead to death	Pharmacoepidemiology studies including a cohort study and case-control study, and specified use-cases surveillances
Important potential risks	- Safety review of long-term administration - Review of increased risk of possible AE - Review of AEs which may occur in the natural course of the underlying disease or complication, and are difficult to distinguish from ADRs - Review whether the frequency of ADR is potentially higher than that of the other drug	long-term administration surveillance/studies, Pharmacoepidemiology studies including a cohort study and case-control study
Important missing information	- Review of the drug safety in the case that safety information obtained from clinical practice by the time of approval was extremely limited due to the inefficient number of patients - Review of the drug safety in the case that the drug may be used in sub-groups including pregnant women.	Information gathering by registry, other active surveillances, use-cases surveillances

2-2.Additional measures based on the post-marketing situation

If an important Safety Specification was newly identified (e.g. severe and fatal ADR is identified by the ADR reports in post-marketing phase), the MAH may be required to take an additional action on risk minimization as well as conducting an additional pharmacovigilance practice to evaluate implementation of the action. When the AE with high background incidence rate due to the natural course of the primary disease and complication is difficult to distinguish from the ADR, in the treatment population, the MAH may be required to conduct an additional pharmacovigilance practice.
When the MAH updates the Phramacovigilance Plan, it should be reflected Safety Specification based on the result newly obtained by the pharmacovigilance.
If an important Safety Specification is newly identified and the MAH conducts an additional action for Pharmacovigilance Plan and risk minimization activity based on the new safety specification, the MAH should preliminarily consult with the regulatory authority.

3. Specific implementation plan for an additional Pharmacovigilance plan

In case of the MAH takes an additional action of pharmacovigilance, the MAH should make an implementation plan which describes the following elements, when the MAH develops or revises the "Basic plan of PMS". And the MAH should make a list of an outline of the plan on each implementation plan basis. When the MAH deals with some Safety Specifications for an identical survey or study, the MAH should describe the items of the Safety Specifications as the issues of the product safety. When the MAH collects information regarding the efficacy of the drug as stated in the chapter 5 from the idetical survey or study as that of safety issues, the MAH should describe it as the same plan.
In the case of clinical trials, the MAH should include details of the monitoring regarding safety concerns (e.g., the rule of clinical trial suspension, information provision to the advisory committee on safety monitoring and timing of implementation of the interim analysis) in the implementation plan.
In addition, the MAH should report the status of the implementation of the Pharmacovigilance Plan on the periodic safety reports.

Details of the implementation plan regarding the safety issues of the product

Safety Issues
Proposed implementation plan
The objective of the proposed implementation plan
Theoretical evidence of the proposed implementation plan
An Additional action which has a potential to be adopted depending on the result and the decision standard to initiate the additional action
Scheduled date of an assessment and report and the reason for fixing the date
Title of an implementation plan (Attach the full text of the implementation plan)

4. The list of a Pharmacovigilance plan/ the summary of ongoing pharmacovigilance practices including a scheduled activity

   For studies which are ongoing or in the planning stage of action, the MAH should make a list describing the status of the implementation and the schedule of preparing the report. The MAH should describe the action in practicing and planning with the milestone and schedule.

Scheduled date of the planned and ongoing Surveillance/ study

Surveillance / study	The number of cases to be a milestone/ target number of cases	The date to be a milestone, the date for an interim report Scheduled closing date	Progress status	Scheduled date for making the result report

For each surveillance and study, the milestone allows the MAH to manage the progress of the Pharmacovigilance Plan, preliminarily evaluate the result and review the plan, so that the MAH can achieve the goal in a timely manner when the MAH reviews some safety specifications simultaneously by the identical Pharmacovigilance Plan (e.g., prospective cohort study). When the MAH sets up milestones, the following should be considered:

- When will AEs with pre-defined frequency at the predetermined reliability level be detected? The MAH should define the frequency reflecting the acceptable level of the patients and public health.

- When will the MAH be able to evaluate accurately the risk factors which affect to onset of AEs?

- When will the result of ongoing or proposed safety study be available?

- When will the assessment of the severity and significance of the risk that is included in Risk Minimization Plan be performed? If the risk is extremely severe, it is necessary to assess the effect of risk minimization activity early in a frequent manner.

V. Surveillances and studies in Drug Efficacy

The MAH should take into account collecting information on drug efficacy, when suggesting draft pharmacovigilace plan.

VI. The Risk Minimization Plan

1. Overview of the Risk Minimization Activity

The Risk minimization plan refers to the overall individual activities for risk minimization. The MAH should contribute to mitigate risks, while maintaining a favorable benefit-risk balance, based on the drug safety information obtained by the time of approval and through the post-marketing pharmacovigilace plan under the RMP and the assessment of that information. The individual risk minimization activity is classified as (□) a routine activity for every product or (□) an additional activity for a specific product. This guidance mainly focuses on an additional risk minimization activity.

2. Routine Risk Minimization Activity

A routine risk minimization activity, which involves all medicinal products, includes preparation and dissemination of a package insert as well as establishment of "indications," "Dosage and Administration" and "Precautions."

3. Additional Risk Minimization Activity

An Additional risk minimization activity for a specific product includes provision of further information to healthcare professionals, preparation and provision of educational materials for patients and establishment of specific conditions of the drug use. It is noted that this section doesn't include a Dear Healthcare Professionals (DHCP) letter.

3-1. Provision of additional information to healthcare professionals

3-1-1. Provision of additional information obtained through EPPV

EPPV is a vigilance which intends to mitigate the harm of the ADR by collecting information on serious ADRs and taking necessary safety measures, as well as ensure to provide information and advise caution for healthcare professionals in order to promote understanding proper use of drugs during the first six months from the time of approval. As a rule, EPPV involves new drugs. (See Notification No.0324001 dated March 24, 2006“Implementation of Early Post-Marketing Surveillance for Prescription Drugs”* issued by Director of Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)

3-1-2. Preparation and provision of materials for proper use

The MAH may decide (or MHLW may require the MAH) to prepare and distribute

additional materials to provide further information included in a package insert, which inform healthcare professionals about proper use of following drug.

- A product that has “Warnings” in a package insert

- A product to be given special attention for proper use (e.g., a product that has "Precautions of indications" or "Precautions of Dosage and Administration")

3-1-3. Promotion of subscription to Pharmaceuticals and Medical Devices Information E-mail Alert Service

Healthcare professionals should be able to surely access the drug proper use information including DHCP letter and revision of Precautions in the package insert. Therefore, the MAH may ask healthcare professionals who use the drug to subscribe to E-mail Alert Service by PMDA (PMDA med-navi).

3-1-4. Publication of pharmacovigilance information on the MAH Website in a timely manner

The MAH should release of the ADR reports and update that in an appropriate timing, when particular attention should be exercised. The MAH also work in collaboration with MHLW, PMDA and involved academic associations to provide information.

3-1-5. Others

The MAH may decide (or MHLW/PMDA may require the MAH during the drug approval process) to prepare and distribute additional materials including the detailed Precautions and SmPC of the new drug, if necessary. The MAH may also use guidelines developed by third parties including academic associations.

3-2. Preparation and provision of an educational material for patients

3-2-1. Medication guide for patients

A Medication guide for patients is prepared so that patients and caregivers could understand the drug properly to identify serious adverse drug reactions early, which provides essential information using easily comprehensible expressions for patients based on the package insert. The MAH prepares the guide of the following drugs to post on PMDA Website. Healthcare professionals may also provide the guide to patients, if necessary. (See Notification No.06300001 dated June 30, 2005 "*Development of the Medication guide for patients" issued by Director of

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

- A product that has “Warnings” in a package insert.

- A product that has "advice for a patient" in sections of Precautions of Indications, Precautions of dosage and Administration or Important Precautions to prevent serious adverse reactions.

- A product of which Healthcare professionals particularly provide patients information on proper use.

3-2-2. Others

Based on a consideration or a requirement by MHLW in the process of drug approval review, the MAH may decide to prepare and provide of another materials that describe individual precautions according to a property of the drug (e.g., a handbook for patients), while making the most of a medication guide.

3-3. Establishment of conditions of the drug use

The MAH should establish the following conditions of the drug use to ensure proper and safety use of the drug according to the property of the drug or the nature of the disease. The MAH should take appropriate measures for the manufacture and distribution of the product (i.e. the MAH will supply the products only to the health institutions that ensure to meet preliminarily set conditions.). These conditions include a description in a package insert (Precautions section) and a setting as an approval condition or a part of the safety control procedure.

3-3-1. Expertise and experience of physicians (and other Healthcare professionals)

The MAH should ask physicians to have high expertise and experience on the treatment of the disease, when the drug has a narrow therapeutic range or a possible serious adverse reaction. The MAH may also ask physicians to take part in the registration, when a particular administration technique is essential. For that, the MAH should preliminarily define requirements including participation in a training seminar to ensure physicians' expertise and experience.

e.g.)

- The MAH asks physicians to participate in the training seminar and ensure expertise and experience regarding the product for the photochemotherapy.

3-3-2. Administration system of drug use

The MAH should ask healthcare professionals to use following drugs only in a health institution where a sufficient emergency treatment is available or in hospitalization setting;

- A drug that has possible serious adverse reactions leading to death.

- A drug that needs strict monitoring after administration.

The regulatory authority may ask the MAH to ensure an administration system for the drug that needs a particular administration system such as a strongly teratogenic drug. In addition, the regulatory authority may ask physicians and pharmacists to take part in the registration.

e.g.)

- For a drug that might cause a blood disorder including agranulocytosis in an early phase of the treatment, the MAH should ask healthcare professionals to use the drug only in a hospitalization setting for a certain period after starting the treatment.

- Regarding a strongly teratogenic drug, the MAH should ask healthcare professionals to limit dispensing the prescribed drug only in a hospital. The MAH may also ask the physicians, pharmacists and patients to participate in the MAH registration, so that they can understand a safety measure thoroughly and conduct more precautionary measures.

3-3-3. Identify of eligible patients for the treatment

Some drugs need to carefully identify eligible patients for the treatment to ensure efficacy and safety of the drugs. The MAH should establish conditions for carefully identifying of patients for the treatment according to disease status, previous history of the disease and therapy or a concomitant drug. The regulatory authority may require the MAH to include patients in the registration, distribute a check sheet to healthcare professionals, check patient eligibility preliminary for the treatment and conduct monitoring, when special attention should be paid.

e.g.)

- The MAH should ask physicians to carefully identify eligible patients for an antineoplastic therapy that has potential adverse reactions relative more frequently observed among specific populations.

3-3-4. Informed consent to a patient before therapy

The MAH should set up some conditions that healthcare professionals should thoroughly inform patients of the drug efficacy and safety and that they should obtain the patients' consent before starting therapy, regarding following drugs;

- A drug that has relative high risk of a fatal adverse reaction. Patients need to be aware of the risk, so that they can find the adverse reaction in early phase and contact their physicians promptly.

- A drug that seems to have a potential risk as specified biological products

The MAH may provide an educational program for patients to avoid a certain serious adverse reaction, help patients thoroughly understand of the therapy and encourage to be more careful for the risk.

e.g.)

- Healthcare professionals should ask patients informed-consent to administration of the antirheumatics that cause a potential serious infection.

- The MAH should ask healthcare professionals to educate patients of the way of drug use and precautions to avoid a certain adverse reaction, regarding a therapy with drug for a self injection.

3-3-5. A specific examination

The MAH should set up some conditions that physicians should give the patient a specific examination to avoid a certain expected adverse reaction.

e.g.)

- The MAH should ask healthcare professionals to perform a peripheral blood test before and regularly during the therapy to avoid a fatal adverse reaction due to bone marrow depression of antineoplastics.

- The MAH should ask healthcare professionals to perform a pregnancy test before starting therapy with a strongly teratogenic drug.

- The MAH should ask healthcare professionals to perform a hepatic function test before and regularly during the treatment with a drug that has relative high incidence of a hepatic function disorder.

3-4. Others

3-4-1. The MAH should take an appropriate measure about a labeling or container / package in the light of avoiding a human error.

e.g.)

- The MAH should improve a PTP design to include the scheduled date of taking of an oral antirheumatic agent that has a complicated dosage schedule.

4. Implementation of an additional risk minimization activity

The MAH should develop or revise a "Basic plan of PMS" to include an implementation plan described in the following, when the MAH conducts an additional risk minimization activity for an individual drug. Further, the MAH should prepare a summary of the every implementation plan like a following table showing.

- Contents, objectives and specific plans of an additional risk minimization activity.

- Basis of an additional risk minimization activity (approval condition, requirement during the assessment and others).

- How to follow up of an additional risk minimization activity.

The MAH should also submit a report of additional risk minimization activities in a Periodic Safety Update Report (PSUR)

safety consideration	
Contents of an additional risk minimization activity	
Objectives of an additional risk minimization activity	
Specific plans of an additional risk minimization activity	
Basis of an additional risk minimization activity	
How to follow up of an additional risk minimization activity	
Reason for the way to follow up of the additional risk minimization activity	

VII. Time of review

It is important that the MAH should review the RMP in an appropriate manner at proper time. The MAH should conduct a review at every milestone in the light of the characteristics of a drug. The milestones of individual drug include below, which the MAH must preliminarily define;

1. At submission of the PSUR

2. At the time of an application for reassessment

3. When the MAH take further safety measures for emerging risk in post marketing setting (e.g., when the MAH revises Precautions with Warnings or Important Precautions)

4. At the time of completion of a surveillance or study for safety

VIII. Report and assessment

1. The MAH should periodically submit a report of a drug safety and efficacy in a safety Pharmacovigilance Plan and Risk Minimization Plan through a periodic report such as PSUR according to the “Basic Plans of PMS”.

2. The MAH should consider and assess the benefit-risk of a drug in a periodic report, based on methods and results of the major surveillances or studies of efficacy and safety and spontaneous adverse reactions reports described in the report.

3. The MAH should review safety issues, the Pharmacovigilance Plan and the RMP included in the “Basic Plans of PMS” at submission of a periodic report described in (1).

4. Regarding a drug that has the RMP and a specific condition for the use, the MAH should submit a report about the RMP implementation and an assessment for its impact at submission of the above periodic report. And then, the MAH should consider revision of the RMP to improve the effectiveness, and discuss with the regulatory authority if necessary.

5. The regulatory authority should consider the report of (1), and may require or ask the MAH to take an appropriate measure.

Provisional translations

* “Implementation of Early Post-Marketing Surveillance for Prescription Drugs”
* Development of the Medication guide for patients" issued by Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)