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Administrative Notice
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To: Prefectural Health Departments (Bureaus)

Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Pharmaceutical Safety Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Questions and Answers (Qs and As) on Risk Management Plan

Handling of Risk Management Plans has been described in “Risk Management Plan Guidance” (PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2 dated April 11, 2012, joint Notification by the Director of Safety Division and the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (hereinafter referred to as MHLW)) and “Risk Management Plan templates and instructions” (PFSB/ELD Notification No. 0426-2 and PFSB/SD Notification No. 0426-1 dated April 26, 2012, joint Notification by the Director of Evaluation and Licensing Division and the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW), and questions and answers to these notifications have been described in “Questions and Answers (Qs and As) on Risk Management Plans” (joint Administrative Notice dated December 5, 2017 by the Pharmaceutical Evaluation Division and the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW) (hereinafter referred to as “previous administrative notice”) and “Points to Consider (Qs and As) on Preparation of Documents for Minor Changes of Risk Management Plans (joint Administrative Notice dated May 10, 2019 by the Office of Pharmacovigilance I and Office of Pharmacovigilance II, Pharmaceuticals and Medical Devices Agency) (hereinafter referred to as “Qs and As on minor changes”). Herein, the contents of the previous administrative notice have been reviewed in association with the issuance of “Risk Management Plan templates, instructions and publication” (PSEHB/PED Notification No. 0318-2 and PSEHB/PSD Notification No. 0318-1 dated March 18, 2022, joint Notification by the Director of Pharmaceutical Evaluation Division and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW). In

association with the abolition of the Qs and As on minor changes, the previous administrative notice and the Qs and As on minor changes have been newly organized and are integrated into the Questions and Answers (Qs and As) as shown in the appendix. Please understand this matter, and inform the relevant organizations under your jurisdiction as a reference for operations.

This administrative notice should apply from May 1, 2022. In addition, the previous administrative notice will be abolished with the application of this administrative notice.

(Appendix)

Questions and Answers (Qs and As) on Risk Management Plan

<Developing the Risk Management Plan>
(Preparation at the time of approval application)

Q1.
In the “Risk Management Plan Guidance,” the “1.2 Scope” includes “At the time of submission of approval application for new drugs.” Is it acceptable to consider that new drugs mentioned here include drugs with a new active ingredient, drugs with a new indication, new dosage drugs, etc. for which a re-examination period is expected to be given?

A1.
The Risk Management Plan (hereinafter referred to as “RMP”) is to be confirmed in the process of approval review, and therefore submission of a draft RMP is necessary at the time of approval application for new drugs regardless of whether or not a re-examination period is given. In principle, new drugs in “1.2 Scope” in the “Risk Management Plan Guidance” correspond to a new active ingredient, new ethical combination drugs, drugs with a new administration route, drugs with a new indication, drugs in new dosage forms, and new dosage drugs in “Drug Approval Application.” (PFSB Notification No. 1121-2 dated November 21, 2014 by the Director of Pharmaceutical and Food Safety Bureau, MHLW) However, please consult with the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) in advance as necessary.

Q2.
Is it necessary to submit a draft RMP as an attached document for approval application for drugs intending addition of a dosage form only?

A2.
No.

Q3.

For new drugs, it is stipulated that a draft RMP should be submitted as an attached document for approval application. When making an application based on public knowledge in accordance with “Handling of Prescription Drugs for Off-label Use” (No. 4 of the Research and Development Division and PMSB/ELD Notification No. 104 dated February 1, 1999, joint Notification by the Director of Research and Development Division, Health Policy Bureau and the Director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHLW) or when making approval applications for products which have completed a prior evaluation for public knowledge-based applications at the Evaluation Committee on Unapproved or Off-Labeled Drugs with High Medical Needs, is it necessary to submit a draft RMP as an attached document for approval application?

A3.

For products for which an RMP has not been published, it is not necessary to newly prepare a draft RMP at the time of application in principle because the indications, etc. related to the application are publicly known in the medical and pharmaceutical fields. It should be described briefly in Module 1.11 of the Common Technical Document (CTD) at the time of application. If the application data are not in CTD format, it is acceptable to omit the description. However, it may be necessary to submit a draft RMP when additional measures are determined to be necessary in the process of approval review. For a product for which an RMP has been published or in a case where the applicant determines that additional measures are necessary at the time of application, a draft RMP should be submitted at the time of application.

When a draft RMP is submitted, it should be submitted in accordance with Attachment 2. of “Risk Management Plan templates, instructions and publication” (PSEHB/PED Notification No. 0318-2 and PSEHB/PSD Notification No. 0318-1 dated March 18, 2022, joint Notification by the Director of Pharmaceutical Evaluation Division and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)).

Q4.

In a case of approval application of a combination product, is it necessary to submit multiple drafts of an RMP for each active ingredient?

A4.

One draft RMP should be submitted for a combination product. For the identification of the safety specifications, the risk of each active ingredient should be considered in addition to the risks of combination or co-administration.

(Preparation at the time of partial change application or after marketing)

Q5.
For products for which an RMP has not been submitted, when is it necessary to submit a new RMP to the PMDA except for the time of application for approval of partial changes in approved items (hereinafter referred to as “partial changes”)? In this case, how should procedures be implemented, including the schedule such as the timing of submission?

A5.
On and after April 1, 2013, cases such as implementing additional activities due to identification of new safety concerns after marketing are applicable. If it is considered necessary to submit a new RMP, the timing of implementation of additional activities to be newly implemented and the timing of submission of an RMP should be consulted with the PMDA in advance. For the part of the submitted RMP other than the description of the additional activities to be newly implemented, the PMDA will inform the applicant of the presence or absence of problems within three months after the submission.

Q6.
For approved drugs for which an RMP has not been submitted, is it acceptable to omit the description about the approved indications, etc., when a draft RMP is prepared at the time of a partial change application?

A6.
In principle, an RMP is prepared for each active ingredient. Therefore, necessary contents should be described for the approved part as well, when a draft RMP is prepared at the time of making a partial change application.

Q7.
For products for which an RMP has not been submitted, how should the contents related to approved indications, etc. be described in the draft RMP to be newly prepared, when it becomes necessary to prepare a draft RMP due to new safety concerns after marketing or a partial change application is made?

A7.
Safety specifications should be identified based on review reports related to approved items and the latest electronic package insert, etc.

Regarding pharmacovigilance activities, surveillance and studies for efficacy, and risk minimization activities, only activities that are ongoing or planned at the time of developing the RMP should be described in the sections of “1. Summary of the RMP,” “2. Summary of the pharmacovigilance activities,” “3. Summary of the plans for surveillance and studies for efficacy,” “4. Summary of the risk minimization plan,” and “5. Lists of the pharmacovigilance plan, surveillance and studies for efficacy, and the risk minimization plan.” In this regard, for the summary of ongoing pharmacovigilance activities and surveillance/studies for efficacy, necessary contents including the timing to reach milestones should be

described based on the Post-Marketing Surveillance and Study Basic Plan that have been already submitted. In addition, for activities ongoing at the time of developing the RMP, an explanatory note should be added to “Implementation status” of each activity described in “5. Lists of the pharmacovigilance plan, surveillance and studies for efficacy, and the risk minimization plan” of RMP, and it should be described in the margin that “the activity has been started before developing the risk management plans.”

Q8.
When a new partial change application is made while a partial change application is under review, should all contents related to the applied indications, etc. be described in the draft RMP to be submitted at the time of application?

A8.
It is desirable to submit a draft RMP that also reflects the contents related to the indications, etc. under review because it is necessary to compile them as one RMP eventually.

(Electronic Package Insert and RMP)

Q9.
Is it correct to understand that it is not necessary to include all of the safety specifications in the Precautions in the electronic package insert?

A9.
Since it is not necessarily required to describe all of the safety specifications such as important potential risks in Precautions, it should be determined individually.

Q10.
For products for which an RMP has not been submitted, is it correct to understand that it is not necessary to include all of the contents described in the Precautions in the electronic package insert in the safety specifications, when it becomes necessary to submit a draft RMP due to a partial change application or identification of new safety concerns after marketing?

A10.
It is not necessary to include all of the contents described in the Precautions in the safety specifications. It should be determined individually in light of “Risk Management Plan Guidance.” (PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2 dated April 11, 2012, joint Notification by the Director of Safety Division and the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW)

(Description methods)

Q11.
How should safety specifications be described if one active ingredient has different safety specifications depending on the indications, etc.?

A11.
A single RMP should be prepared for a product containing one active ingredient with different indications, dosage and administration, dosage forms, route of administration, etc. The contents of the safety specifications should be described in a way to make it clear that the contents differ depending on indications, etc., using an explanatory note, etc. However, if the safety specifications differ significantly depending on the indications, etc., an RMP can be prepared separately.

Q12.
In the “due date for preparation of the report” column of “Additional pharmacovigilance activities” in “5.1 A list of the pharmacovigilance plans” of an RMP, which date should be described, the due date for preparation of the report as a re-examination material or the date when the results of the vigilance activities are compiled within the company?

A12.
For individual surveillance, studies, etc. as pharmacovigilance activities, it is necessary to prepare a report promptly when the results are obtained and to examine whether further necessary measures should be taken based on the evaluation results. Therefore, the date when the marketing authorization holder compiles the results for each surveillance, study, etc. should be described regardless of the date of the re-examination application.

Q13.
What are the additional activities that need to be described in the RMP?

A13.
Concerning additional pharmacovigilance activities or surveillance/studies for efficacy, post-marketing surveillance, etc., which are judged to require implementation during the process of approval review or after marketing, should be described in the RMP, among those scheduled to be implemented by marketing authorization holders. In principle, no description is required for surveillance and studies conducted voluntarily by the marketing authorization holder.

Additional risk minimization activities to be implemented by the marketing authorization holder should be described in an RMP, such as preparing and distributing materials to provide information in addition to describing them in the electronic package insert or patient medication guide regarding proper use to prevent the occurrence of serious adverse drug reactions, and registering patients to be treated to ensure the drug use management system. Notifications

prepared and distributed at the time of revision of the electronic package insert that contain the revised contents alone do not apply to the activities above.

On a case-by-case basis, the necessity of description should be consulted with the PMDA in the processes of approval review and post-marketing confirmation, after judgement in light of “Risk Management Plan Guidance” (PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2 dated April 11, 2012, joint Notification by the Director of Safety Division and the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW).

Q14.
What should be included in the efficacy specification?

A14.

Describe the efficacy specification that could not be fully evaluated before approval. For example, the following cases are assumed.

- When it is necessary to collect information on the efficacy of long-term administration because the efficacy may be weakened by long-term administration based on the mechanism of action, etc., while the drug is, after approval, expected to be administered for a long period beyond the treatment period investigated in clinical studies.
- When it is important to investigate the efficacy for a true endpoint because only an exploratory endpoint for efficacy of this drug is shown before approval.

On a case-by-case basis, the necessity of description should be consulted with the PMDA in the process of approval review and post-marketing confirmation. It is not necessary to describe the contents of concerns on indications or dosage and administration outside the scope of approval.

Q15.
Should information collection from clinical studies and surveillance conducted only overseas be described as additional pharmacovigilance activities or surveillance and studies for efficacy?

A15.

No. However, if information from clinical studies and surveillance conducted only overseas are used to examine and evaluate safety and efficacy specifications, descriptions in the sections of safety and efficacy specifications should be considered as necessary.

(Others)

Q16.
Are risks associated with off-label use included in the scope of the evaluation in an RMP?

A16.

In principle, the scope of the evaluation in an RMP is within the range of approval. However, there are cases where it is necessary to evaluate whether to

include risks associated with off-label use in the scope of an RMP, etc., such as a situation in which special attention should be paid.

Q17.
Where is the consultation contact point of the PMDA on an RMP?

A17.
Consultation on an RMP is responded to by each review team in charge during the approval review and by the Office of Pharmacovigilance I or the Office of Pharmacovigilance II after approval. However, even after approval, if a partial change application is under review, each review team in charge responds to the consultation on the plan within the scope of review.

As for consultation before approval application, consult with the review team in charge by using the clinical trial consultation as is the case with the conventional consultation on post-marketing surveillance, etc.

<Submission, publication, and change of RMP>
(Submission and publication of RMP)

Q18.
For products for which conditions for approval related to development and implementation of an RMP are given, is it necessary to change an RMP when additional pharmacovigilance activities or additional risk minimization activities related to indication A are considered unnecessary at the time of approval of partial changes related to addition of indication A?

A18.
An RMP should be submitted with the summary of products and other relevant sections changed.

Q19.
Since it is desirable to publish an RMP and materials to be prepared and provided for healthcare professionals and patients as additional risk minimization activities promptly after approval, submission is to be made promptly after the completion of the First or Second Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council, which deliberates or reports on the approval of the target drug, in consideration of the confirmation period at the PMDA. How should it be handled if it takes time to prepare attached documents such as materials, etc. used for additional risk minimization activities and Post-Marketing Surveillance and Study Implementation Plans while an RMP itself is ready for submission?

A19.
If it takes time to prepare attached documents such as materials for additional risk minimization activities and Post-Marketing Surveillance and Study Implementation Plans, consider submitting only an RMP first to the PMDA in order to publish an RMP promptly after approval. Even in this case, materials used for

additional risk minimization activities should be submitted and published to avoid a delay as much as possible from the timing of submission and publication of the RMP. As for the Post-Marketing Surveillance and Study Implementation Plan, as a general rule, it should be submitted one month before the timing of the planned start of the surveillance or clinical studies as described in Attachment 3. (2) of the Notification on templates, instructions and publication. Refer to the Qs and As 25 for how to submit attached documents such as materials for additional risk minimization activities and Post-Marketing Surveillance and Study Implementation Plan. On a case-by-case basis, this should be consulted with the PMDA.

Q20.
An RMP should be submitted promptly after the completion of the First or Second Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council, which deliberates or reports on the approval of the target drug, in consideration of the confirmation period at the PMDA, and if it takes time to submit an RMP and attached documents for particular reasons, they should be submitted one month before the timing of the planned product market launch at the latest. In the case of a partial change approval, by when should it be submitted to the PMDA?

A20.
In order to publish an RMP and materials to be prepared and provided for healthcare professionals and patients as additional risk minimization activities at the time of a partial change approval, an RMP should be submitted promptly in consideration of the confirmation period at the PMDA, following the First or Second Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council, which deliberates or reports on the approval of the target drug. Among biosimilar products, in the case of a partial change approval which does not go through the First or Second Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council, an RMP should be submitted promptly after completion of the review of the product.

Q21.
If an RMP is submitted before the approval date, when should the RMP be published? In addition, what date should be entered, at each submission and publication time, in the “Date of submission” in Appended Form 2 of the Notification on templates, instructions and publication?

A21.
An RMP should be published on and after the approval date. When an RMP is submitted to the PMDA before the approval date, the date of submission should be described in the “Date of submission” in Appended Form 2 of the Notification on templates, instructions and publication. If the RMP is published after completion of confirmation by the PMDA, additions or changes of the additional

information at the time of approval (Date of market authorization, Therapeutic category, Re-examination period, Approval number, International birth date, Strengths and dosage form, Dosage and administration, Indication, Conditions for approval, etc.) in the “Outline of the product” column of the RMP should be made as minor changes, based on the Qs and As 26. The date of the minor change should be described in the “Date of submission” of Appended Form 2 of the Notification on templates, instructions and publication.

Q22.
In the case of transition from a clinical trial to a post-marketing clinical study after approval, is it necessary to submit an RMP and protocol one month before approval?

A22.
When a clinical trial is transited to a post-marketing clinical study at the time of approval, it is not necessary to submit the post-marketing clinical study protocol to the PMDA by one month before the start of the study if described as such in the remarks column of the clinical trial notification. The post-marketing clinical study protocol for the study should be submitted when the RMP is submitted. It is not necessary to submit the post-marketing clinical study protocol in advance, but preparation, storage, etc. of the post-marketing clinical study protocol are continuously necessary based on the “Ministerial Ordinance on Good Clinical Practice for Drugs” (MHW Ordinance No. 28 in 1997), etc.

Q23.
Is it possible to submit an RMP before the date of drug succession in order to publish the RMP and the materials to be prepared and provided for healthcare professionals and patients as additional risk minimization activities promptly after the date of succession of the drug?

A23.
It is possible to submit an RMP before the date of drug succession, if a notification of approval succession has been already submitted to the PMDA. An RMP should be published on and after the date of succession. When an RMP is submitted to the PMDA before the date of succession, it should be described in the “Remarks” column of Appended Form 1 of the Notification on templates, instructions and publication that this drug is to be succeeded, and the date of the submission should be described in the “Date of Submission” column of Appended Form 2. When publishing an RMP after the completion of confirmation by PMDA, additions or changes of the additional information at the time of succession in the “Outline of the product” column of the RMP, or deletion of the notice that this drug is to be succeeded in the “Remarks” column should be made as minor changes, based on this Qs and As 26. The date of the minor changes should be entered in the “Date of Submission” column of Appended Form 2 of the Notification on

templates, instructions and publication. Consult with the PMDA in advance as necessary.

(Changes in RMP)

Q24.
When a “Conventional Post-Marketing Surveillance and Study Basic Plan” is changed or added on and after April 1, 2013, is it reasonable to submit it in the form of a change notification or addition notification for the “Conventional Post-Marketing Surveillance and Study Basic Plan”?

A24.
Unless an RMP is newly prepared for reasons such as identification of new safety concerns after marketing, it may be handled as before. However, if new safety concerns are identified and changes are to be made, consult with the PMDA.

Q25.
When changes are made in an RMP, the latest RMP should be submitted to the PMDA except for minor changes. By when should the RMP after changes be submitted? Also, what documents should be submitted?

A25.
They should be submitted in accordance with the following depending on the item to be changed. In either case, it is desirable to consult with the PMDA in advance as necessary.

1. If any safety or efficacy specifications are added, deleted, or changed:
   The latest changed RMP should be promptly submitted to the PMDA.

2. Items related to pharmacovigilance activities or surveillance/studies for efficacy
   1) When pharmacovigilance activities or surveillance/studies for efficacy are newly added:
      The latest changed RMP should be submitted to the PMDA by one month before the planned start time of the activity or surveillance/studies.
   2) When the contents of ongoing pharmacovigilance activities or surveillance/studies on efficacy are changed (including the case where the Post-Marketing Surveillance and Study Implementation Plan is changed, excluding minor changes):
      The latest changed RMP should be submitted to the PMDA by one month before the time when the contents of the activities or surveillance/studies will be changed.
   3) When pharmacovigilance activities or surveillance/studies for efficacy are completed:

After submitting to the PMDA a report compiling the results related to the activities or surveillance/studies as an implementation report for the early post-marketing phase vigilance, periodic safety update report, or evaluation report on the RMP, the latest changed RMP should be promptly submitted to the PMDA.

3. Items related to risk minimization activities
   1) When a new risk minimization activity is added:
      Consult with the PMDA before changing the RMP.
   2) When the contents of the ongoing risk minimization activities are changed (excluding minor changes):
      Concerning significant changes, consult with the PMDA before changing the RMP. In other cases, the latest changed RMP should be promptly submitted to the PMDA.
   3) When risk minimization activities are completed:
      The latest changed RMP should be promptly submitted to the PMDA.

The PMDA will inform the applicant of the presence or absence of problems within one month after the submission of the latest RMP.

Documents should be submitted in accordance with the following.

- If there is any change in an attached document of an RMP, or an attached document is submitted afterwards following an RMP which is submitted in advance in accordance with the Qs and As 19 and 38, the outline of the contents of the changes should be described in the column of change history in Appended Form 1 of the Notification on templates, instructions and publication. Documents specifying the details of the contents of the changes (old/new comparison tables, etc.) and the changed attached document should be submitted at the same time. Besides, if necessary, submission of documents specifying the details of contents of changes may be requested for documents to be attached.
- If there is no change in the documents that have been submitted as attached documents, it is not necessary to submit them each time the RMP is changed. In that case, it should be stated in the section of “Document number” in “Attached document” in Appended Form 3 of the Notification on Risk Management Plan templates, instructions and publication that they have been already submitted.

(Minor changes in RMP)

Q26. In Attachment 5. of the Notification on templates, instructions and publication, it is stated “When changes are made in an RMP, the latest RMP should be submitted to the PMDA except for minor change.” What is the case with “minor change” that does not require submission?

A26.

A “minor change” is applicable only to cases where there is no substantial impact on the contents of the RMP. Typical examples of “minor change” are shown below. If it is difficult to determine the range of “minor change,” consult with the PMDA as necessary.

1. Changes related to RMP

- Correction of errors or changes of terms that does not result in a change in the meaning
- Change of a company’s name alone, excluding succession
- Addition or change of a brand name alone in the “Outline of the product” column of the RMP (e.g., addition of a brand name associated with addition of a dosage form)
- Deletion of a brand name alone in the column of “Outline of the product” associated with approval withdrawal.
- (In case that an RMP has been submitted before approval) Addition or change of additional information at the time of approval (Date of market authorization, Therapeutic category, Re-examination period, Approval number, International birth date, Strengths and dosage form, Dosage and administration, Indication, Conditions for approval, etc.) in the “Outline of the product” column of the RMP. If the said minor change is made at the time of preparing a new RMP, it is not necessary to describe the contents of changes in the “Change history” or underline the changed parts. If the said minor change is made for a product for which changes occur in the existing RMP due to a partial change approval, the contents of changes due to a partial change approval should be described in the “Change history,” and the changed parts should be underlined.
- (In case that an RMP has been submitted before succession) Addition or change of additional information at the time of succession in the “Outline of the product” column of RMP, or deletion of the notice that this drug is to be succeeded in the “Remarks” column.
- Deletion of descriptions, after the early post-marketing phase vigilance report is received by the PMDA, regarding the early post-marketing phase vigilance in “2. Summary of the pharmacovigilance activities” and “4. Summary of the risk minimization plan,” as well as change of the “Implementation status” column of the early post-marketing phase vigilance in “5. Lists of the pharmacovigilance plan, surveillance/studies for efficacy, and the risk minimization plan.”
- Change of the “Implementation status” column in “5. Lists of the pharmacovigilance plan, surveillance and studies for efficacy, and the risk minimization plan” (e.g., change from “To be implemented from XX” to “Ongoing”) due to start of post-marketing surveillance, etc.

2. Changes related to implementation plans for post-marketing surveillance, etc. regarding additional pharmacovigilance activities and surveillance/studies for efficacy

- Correction of errors or changes of terms that do not result in a change in the meaning
- Change of the start date of the surveillance regarding the scheduled implementation period, due to postponement of the start of marketing,
- Change of the planned number of sites
- Changes of the layout of the survey form, implementation guideline, and registration form (e.g., changes of the position of description items, changes of the size of the entry column
- Changes, additions, and deletions of the name and address of the contractor, and the scope of the duties outsourced
- Changes of the organizational structure for conducting operations of post-marketing surveillance, etc.
- Addition or change of a brand name alone of a drug to be surveyed in implementation plans (e.g., addition of a brand name associated with addition of a dosage form)

3. Changes related to materials, etc. used for additional risk minimization activities

- Correction of errors or changes of terms that do not result in a change in the meaning
- Changes of design not associated with change of contents or emphasis (changes of size of material, color tone (excluding color of text), change of illustration, etc.)
- Addition or change of a brand name alone of a drug to be surveyed in a material (e.g., addition of a brand name associated with addition of a dosage form)

Q27.
If a minor change is made to an RMP and attached documents, is it acceptable to reflect the contents of the minor change at the next submission of an RMP accompanied by the relevant change in the document?

A27.
Yes.

Q28.
What should be entered in “Date of submission” in Appended Form 2 of the Notification on templates, instructions and publication?

A28.
For an RMP submitted to the PMDA, enter the date of submission. For an RMP with minor changes, enter the date when the RMP with the minor changes is

posted on the website of the PMDA. Regarding what date to enter in the “Date of submission” in a case where an RMP is submitted before approval and published after approval, or where an RMP is submitted before succession and published after succession, refer to the Qs and As 21 and 23.

Q29.
What date should be entered in the “Date of previous submission” in the change history column of an RMP?

A29.
Enter the “Date of submission,” which is described in Appended Form 2 of the Notification on templates, instructions and publication of the most recently published version of an RMP (the date of submission if the most recently published version of an RMP has been submitted to the PMDA, or the date of posting on the website of the PMDA if a minor change has been made to the RMP).

Q30.
In the case of a minor change, what should be described in the “Summary of the changed contents” in the change history column of an RMP? Is it necessary to underline the changed parts of an RMP?

A30.
In the “Summary of the changed contents” in the change history column of an RMP, describe that it is a minor change as well as the changed contents.

Even if minor changes have been made in the most recently published version of the RMP, it is required only to describe, in the “Summary of the changed contents” of the most recently published version of the RMP, the changes from the most recently published version of the RMP and the fact that they are minor changes. It is not necessary to comprehensively describe the history of minor changes after submission of the RMP to the PMDA.

Even in the case of a minor change, the changed part of the RMP should be underlined.

Refer to the Qs and As 26 for what to describe in “Summary of the changed contents” and how to underline the changed parts of the RMP, when an RMP is submitted before approval and published on and after the date of submission with addition or change of additional information at the time of approval in the “Outline of the product” column of the RMP due to minor changes.

Q31.
Is it necessary to change the main body of the RMP even when a minor change is made only for the materials?

A31.

It is also necessary to change the main body of the RMP. In the change history column of the RMP, describe the fact that a minor change has been made to the material as well as the contents of changes in the material.

Q32.

How does the PMDA confirm the contents of minor changes?

A32.

When changes are made in an RMP that requires submission to the PMDA, the PMDA confirms the contents of minor changes made between the previous submission and this submission.

Therefore, if any minor change has been made between the previous submission and this submission, a series of documents in which the details of each change (old/new comparison tables including the contents before and after the changes, history of the amendments, etc.) can be confirmed should be submitted for reference, in addition to the contents of the changes at the time of this submission. In this regard, it is not necessary to describe in the change history column of the RMP the contents corresponding to minor changes made between the previous submission and this submission.

If there are any concerns about the changes that are handled as a minor change as a result of confirmation by the PMDA, the PMDA may request the company to take necessary actions.

Q33.

If there is any change in an RMP (including attached documents) in association with the change in the electronic package insert according to the new instructions*, can the change be handled as a “minor change”?

* “Instructions for Electronic Package Inserts of Prescription Drugs” (PSEHB Notification No. 0611-5 dated June 11, 2021, issued by the Director of Pharmaceutical Safety and Environmental Health Bureau, MHLW)

A33.

Changes related only to changes of sections in the electronic package insert (e.g., changes of description in “Careful Administration” to “9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS”) can be handled as a “minor change.” If there is a change that has a substantial impact on contents of an RMP (including attached documents), the changed RMP (including attached documents) should be submitted to the PMDA instead of treating it as a “minor change.” If it is difficult to make a determination, consult with the PMDA as necessary changes in an RMP should be made promptly after submission of the electronic package insert in accordance with the new instructions.

<RMP for generic drugs>

Q34.
There are two indications A and B for the original drug, and an RMP was published at the time of a partial change approval for the addition of indication B. Regarding development of the RMP for generic drugs, is it acceptable to consider that submission of a draft RMP is unnecessary when an approval application for a generic drug is made only for indication A for the reason that indication B is in the re-examination period or for other reasons?

A34.
Yes. The draft RMP should be submitted at the time of an approval application for indications A and B or a partial change application for addition of indication B.

Q35.
There are three indications A, B and C for the original drug, and an RMP was published at the time of the partial change approval for addition of indication B. At the time of the partial change approval for addition of indication C, no additional pharmacovigilance activities or additional risk minimization activities for indication C were implemented. For generic drugs, is it acceptable to consider that submission of a draft RMP is unnecessary when an approval application is made for indications A and C for the reason that the indication B is in the re-examination period or for other reasons?

A35.
Yes. The draft RMP should be submitted at the time of an approval application including indication B or a partial change application for addition of indication B.

Q36.
There are two dosage forms A and B of the original drug with different dosage and administration (route of administration), etc., and the RMP was published in association with the approval of dosage form B. Is it acceptable to consider that the submission of a draft RMP is unnecessary when an approval application is made for a generic drug of dosage form A?

A36.
Yes. A draft RMP should be submitted when the approval application of dosage form B is made.

Q37.
An RMP of the original drug was published at the time of approval for indications A and B. For the generic drug, an approval application is made only for indication A for the reason that indication B is in the re-examination period or for other reasons. Is it acceptable to consider that submission of a draft RMP is unnecessary?

A37.

Pharmacovigilance activities, surveillance/studies for efficacy, or risk minimization activities including those on indication A have been planned in the RMP of the original drug. Therefore, when an approval application for the generic drug for indication A is to be made, it is necessary to submit a draft RMP that describes matters related to indication A.

Q38.

Since it is desirable to publish an RMP and materials prepared and provided for healthcare professionals and patients as additional risk minimization activities promptly after approval, it is specified that an RMP and attached documents of generic drugs should be submitted to the PMDA promptly after completion of the review. How should it be handled if it takes time to prepare attached documents such as materials for additional risk minimization activities and Post-Marketing Surveillance and Study Implementation Plans while an RMP itself is ready for submission?

A38.

If it takes time to prepare attached documents such as materials for additional risk minimization activities and Post-Marketing Surveillance and Study Implementation Plans, consider submitting only an RMP first to the PMDA in order to publish an RMP promptly after approval. Even in this case, materials used for additional risk minimization activities should be submitted and published to avoid a delay as much as possible from the timing of submission and publication of the RMP. As for the Post-Marketing Surveillance and Study Implementation Plan, as a general rule, it should be submitted one month before the timing of the planned start of the surveillance or clinical studies as described in Attachment 3. (2) of the Notification on Risk Management Plan templates, instructions and publication. Refer to the Qs and As 25 for how to submit attached documents such as materials for additional risk minimization activities and Post-Marketing Surveillance and Study Implementation Plan. On a case-by-case basis, this should be consulted with the PMDA.

Q39.

An RMP of generic drugs should be submitted promptly after the completion of review of the product in consideration of the confirmation period at the PMDA. If it takes time to submit an RMP and attached documents for particular reasons, it should be submitted one month before the timing of the planned product market launch at the latest. In the case of a partial change approval, by when should it be submitted to the PMDA?

A39.

In order to publish an RMP and materials prepared and provided for healthcare professionals and patients as additional risk minimization activities at the time of approval of partial changes, they should be submitted to the PMDA promptly after

completion of the review of the product in consideration of the confirmation period at the PMDA.

Q40.
An RMP of an original drug has not been published at the time of the approval application for a generic drug, and an RMP an original drug for the “indications,” for which the generic drug is applied for approval, is published during the approval review of the generic drug. Is it necessary to submit a draft RMP of the generic drug? If submission is necessary, by when should a draft RMP be prepared and submitted?

A40.
Submission is necessary. It should be submitted within one month after publication of the RMP of the original drug.

Q41.
If the RMP for the original drug is updated, by when should the updated RMP for the generic drug be submitted?

A41.
It should be submitted within one month after publication of the updated RMP of the original drug.

Q42.
When a draft RMP for a generic drug is prepared, is it acceptable to describe it by referring to the RMP for the original drug?

A42.
RMPs for generic drugs should be prepared appropriately after confirming not only the published RMPs for original drugs but also electronic package inserts, review reports, etc.

Pharmacovigilance activities, surveillance/studies for efficacy, and risk minimization activities should be planned in reference to “Milestone date for evaluation of the activities” and “Implementation status” in “5. Lists of the pharmacovigilance plan, surveillance and studies for efficacy, and the risk minimization plan” in the published Risk Management Plan of the original drug.

The reasons for selecting the safety and efficacy specifications, the reasons for selecting pharmacovigilance activities and risk minimization activities should be described based on the latest information.

<Evaluation and report of RMP>

Q43.
Is it acceptable to report the results of reviewing an RMP at the time of submitting periodic safety reports?

A43.

For new drugs during the re-examination period, it is acceptable to report them in the periodic safety reports. However, depending on the contents of the additional pharmacovigilance plan and the risk minimization plan, it may be necessary to separately set an appropriate timing for reporting the results of reviewing an RMP in advance, in addition to the timing of submitting periodic safety reports.

Q44.

How should the results of risk minimization activities be evaluated?

A44.

The evaluation should be performed, to the extent possible, by using the evaluation method such as evaluating the implementation status of risk minimization activities and the occurrence status of cases of adverse drug reactions before and after safety measures, in accordance with the characteristics of the drugs or adverse drug reactions.

Q45.

How will the conditions for approval related to development and implementation of an RMP be handled, if all the activities by marketing authorization holders regarding the additional pharmacovigilance activities and the additional risk minimization activities specified in an RMP are completed?

A45.

The conditions for approval related to development and implementation of RMP will be evaluated by the PMDA at the time of re-examination and handling will be considered. Therefore, the RMP should be continuously reviewed at least at the time of periodic safety reports, and the results should be reported.

Q46.

If an RMP is granted as a condition for approval after completion of re-examination or for a product not subject to re-examination, how should procedures be taken to lift the condition for approval?

A46.

Consult with the PMDA. The PMDA will judge whether or not it is appropriate to consider lifting the conditions for approval, based on the descriptions in reports submitted in accordance with the “Evaluation report after completion of re-examination period based on implementation of risk management plan” (PFSB/SD Notification No. 1220-14 dated December 20, 2013). At the time of the evaluation and deliberation by the PMDA, companies related to the said conditions for approval may be asked to organize and submit necessary information, etc. Usually, after the evaluation and deliberation by the PMDA, it is reported to and approved by the Pharmaceutical Affairs and Food Sanitation Council (First or Second Committee on New Drugs, or Committee on Drug

Safety) of the MHLW, and the propriety of lifting the conditions for approval is determined.

Refer to the Qs and As 49 for the procedures for lifting conditions for approval related to an RMP for a generic drug, which is in association with those for an original drug based on the results of re-examination of the original drug.

<Re-examination and RMP>

Q47.
How should procedures for an RMP be performed in association with re-examination?

A47.

Depending on whether or not re-examination has been completed for the dosage form, indications, etc. other than the indications, etc. subject to the re-examination application, take actions according to the following:

1. When re-examination pertaining to all dosage forms, indications, etc. other than the indications, etc. subject to this re-examination has been completed, or when there are no approved indications, etc. other than the indications, etc. subject to this re-examination.
   1) At the time of application for re-examination:
      It is not necessary to submit the RMP to reflect the fact that the re-examination application is already filed.
      Re-examination application materials should be handled as follows.
      i) If the applicant determines that it is necessary to continue additional activities or conduct new additional activities based on the information collected during the re-examination period, a draft of the changed RMP including these activities should be included in the re-examination application materials.
      ii) If the applicant determines that it is not necessary to continue additional activities or conduct new additional activities based on the information collected during the re-examination period, it is not necessary to include a draft of the changed RMP in the re-examination application materials.
   2) After completion of re-examination (after notification of re-examination results):
      i) If the conditions for approval related to development and implementation of the RMP are judged to be satisfied (when it is judged that it is not necessary to continue additional activities or conduct new additional activities), it is not necessary to change the RMP.
      ii) If it is judged necessary to continue additional activities or conduct new additional activities as a condition for approval for development and implementation of the RMP after completion of re-examination, it is necessary to change the RMP. After the issuance of the notification of re-examination results, the RMP in which the relevant change has been made should be submitted promptly. When making changes, additional

activities for which the evaluation has been completed in re-examination can be deleted from the RMP.

2. When there are indications, etc. for which re-examination has not been completed other than the indications, etc. subject to this re-examination
   1) At the time of application for re-examination:
      It is not necessary to submit the RMP to reflect the fact that the re-examination application is already filed.
      Regarding the re-examination application materials, for the indications, etc. subject to this re-examination, the necessity of continuing additional activities or conducting new additional activities should be determined based on the information collected during the re-examination period, and then a draft of the changed RMP including the contents reflecting the results should be included in the re-examination application materials.
   2) After completion of re-examination (after notification of re-examination results):
      It is necessary to change the RMP based on the re-examination results.
      After the issuance of the notification of re-examination results, the RMP in which the change has been made should be submitted promptly. When making changes, additional activities for which the evaluation has been completed in re-examination can be deleted from the RMP.

Q48.
Will an RMP posted on the website of the PMDA be deleted after completion of re-examination?

A48.

If re-examination pertaining to all dosage forms and indications, etc. is completed and it is judged that the conditions for approval related to development and implementation of an RMP are satisfied, the RMP will be deleted after the issuance of the notification of re-examination results, and the RMP that is published at the time of re-examination application will be published with the re-examination report.

If re-examination pertaining to all dosage forms, indications, etc. is completed and it is judged that the conditions for approval related to development and implementation of the RMP are satisfied, the RMP that is published at the time of the re-examination application should be sent to Review Planning Division, Office of Review Management, based on “Submission of Documents for RMP Publication at the Time of Completion of Re-examination (Request for Tentative Actions)” (joint Administrative Notice of the Office of Review Management and the Office of Informatics and Management for Safety, PMDA, dated January 23, 2020).

Q49.

If conditions for approval related to an RMP for an original drug are lifted as a result of re-examination, how should the conditions for approval of the RMP for the generic drug be lifted?

A49.

When a marketing authorization holder of a generic drug submits a request for lifting conditions for approval to the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW (hereinafter referred to as “Pharmaceutical Evaluation Division”) and it is judged possible to lift the conditions for approval, an administrative notice related to lifting conditions for approval will be issued to the marketing authorization holder. After the conditions for approval are lifted on the basis of the said administrative notice, the marketing authorization holder should delete the RMP of the generic drug from the website of the PMDA. For procedures for lifting individual approval conditions, consult with the Pharmaceutical Evaluation Division.

End of document