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July 18, 2024

To: Directors of Prefectural Health Departments (Bureaus)

Director of Pharmaceutical Evaluation Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Director of Pharmaceutical Safety Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Partial Revision of the "Procedures for Developing Post-marketing Study Plans for Drugs"

The procedures for developing post-marketing study plans have been presented to date by the "Procedures for Developing Post-marketing Study Plans for Drugs" (PSEHB/PED Notification No. 0314-4 and PSEHB/PSD Notification No. 0314-4 dated March 14, 2019 issued jointly by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare and the Director of the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare). Taking into consideration the recent change in the drug discovery environment, international harmonization and the past achievement in the post-marketing safety measures in Japan, it has been decided to revise this notification as shown in the attached old and new comparison table. Please understand the following information, and cooperate in disseminating it to the relevant organizations under your jurisdiction. The revised notification is attached for reference.

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(Attachment) "Procedures for Developing Post-marketing Study Plans for Drugs" Old and New Comparison Table

(Underlined parts indicate revisions.)

After revision	Before revision
(Omitted)	Procedures for Developing Post-marketing Study Plans for Drugs
	Post-marketing study plans consist of study plans for efficacy and pharmacovigilance plans, both of which will be planned when additional surveillance is necessary in the post-marketing phase. When a post-marketing study is conducted, it is important to clarify a research question based on the information obtained from pre-marketing clinical trials, the characteristics of target diseases and the drugs of interest, etc. and to conduct the study properly afterwards. At the same time, it should be noted that the purpose and the necessity of a post-marketing study should be fully considered to prevent the study from being conducted aimlessly. The research question here means a specific and clear aim of a study, including population, intervention (exposure), comparator, outcome (efficacy/safety specifications of interest), and timing. Based on the question, study design, effect measure which will be eventually evaluated, data source, etc. should be carefully considered.
Generally, efficacy data required for the marketing authorization (hereinafter referred to as "approval") are collected from pre-marketing clinical trials and a certain level of evaluation on efficacy is made at the time of approval. Therefore, if any specific concerns about efficacy are not raised during the approval review process or in the post-marketing phase, efficacy could be evaluated with means other than post-marketing studies (e.g., analysis based on literature). On the other hand, if a specific concern about efficacy arises during	Generally, efficacy data required for the marketing authorization (hereinafter referred to as "approval") are collected from pre-marketing clinical trials and a certain level of confirmation on efficacy is made at the time of approval. Therefore, if no specific concerns about efficacy are raised during the approval review process or in the post-marketing phase, effectiveness could be monitored with means other than post-marketing studies (e.g., analysis based on literature). On the other hand, if a specific concern about

the approval review process or in the post-marketing phase, a post-marketing study should be implemented so that the concern can be scientifically verified. (Omitted)	efficacy arises during the approval review process or in the post-marketing phase, a post-marketing study must be implemented so that the concern can be scientifically verified. Safety specifications are set based on the notification "Risk Management Plan Guidance" (No. 0411-1, by the Director of the Safety Division [SD], and No. 0411-2, by the Director of the Evaluation and Licensing Division [ELD], Pharmaceutical and Food Safety Bureau [PFSB], MHLW, dated April 11, 2012). With consideration for a scientific point of view and the current approval review process, development of pharmacovigilance plan can be divided into the following four steps (refer to the figure); 1) concretization of concerns that need to be clarified in the post-marketing phase in each safety specification, 2) determination of a scientifically appropriate approach for each concern, 3) confirmation of legal and regulatory framework where each approach to be compiled, and 4) development of the study protocol. In principle, an applicant should reach an agreement with the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") about Step 1-3 before the approval. The features and points to consider for each step are shown below. In addition, the following MHLW notifications (hereinafter referred to as "the notifications related to pharmacovigilance") should be referred to for consideration of them. ● "Pharmacovigilance planning" (No. 0916001, by the Director of ELD, and No. 0916001, by the Director of SD, PFSB, MHLW, dated September 16, 2005; hereinafter referred to as "ICH E2E Guideline")

	● "Basic Principles on the Use of Medical Information Databases in Post-marketing Pharmacovigilance" (No. 0609-8, by the Director of the Pharmaceutical Evaluation Division, and No. 0609-4, by the Director of the SD, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 9, 2017)
If there is a specific safety concern and a research question can be formulated at the time of approval, a post-marketing study plan will be considered before approval (only its outline may be considered before approval, and a detailed study plan may be considered after approval.). In other cases, however, a post-marketing study plan, including its necessity, will be considered at an appropriate timing not before approval but in the post-marketing phase (when any new research question is developed e.g., when Early Post-marketing Phase Vigilance (EPPV) data are obtained or when a new concern arises and safety information that should be clarified in terms of post-marketing safety measures is obtained). (Omitted)	(Newly established) Early post-marketing phase vigilance (EPPV) is out of scope of this document because EPPV should be planned for each product according to the notification "Implementation Methods, etc. of Early Post-marketing Phase Vigilance for Prescription Drugs" (No. 0324001, by the Director of SD, PFSB, MHLW, dated March 24, 2006) and the administrative notice "Q & A on Early Post-marketing Phase Vigilance for Prescription Drugs" (SD, PFSB, MHLW, dated March 24, 2006).

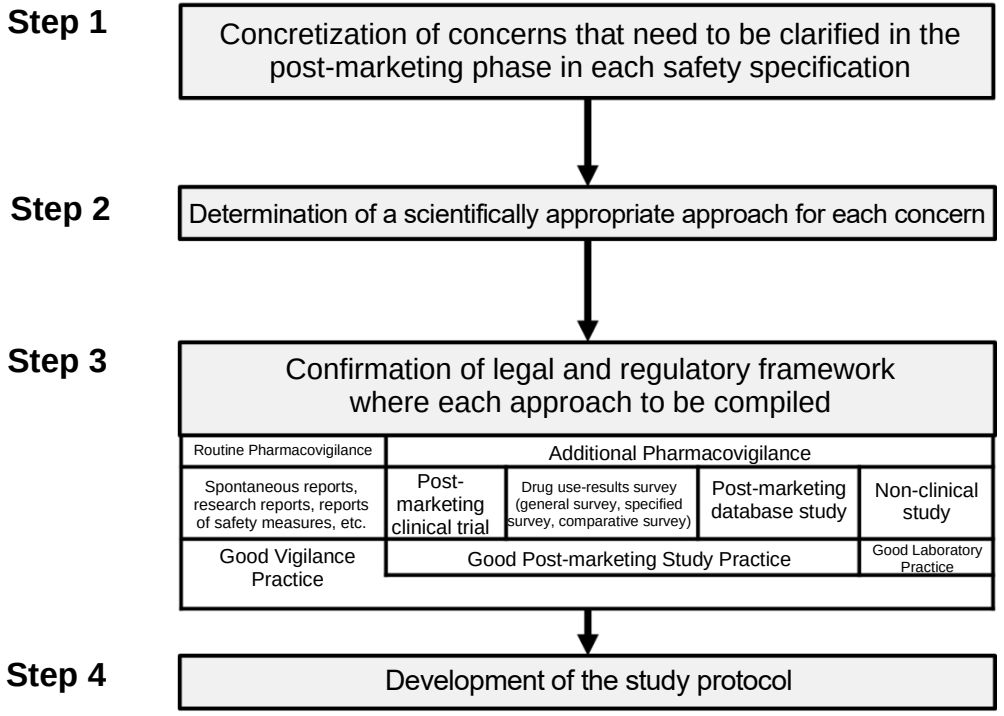

Figure. Overview of the development of pharmacovigilance planning

Step 1) Concretization of concerns that need to be clarified in the post-marketing phase in each safety specification

The first step is to concretize concerns that need to be clarified in the post-marketing phase in each safety specification determined based on the information obtained by the time of approval application (i.e., what should be clarified, what information would be sufficient to judge the necessity and

Step 1) Concretization of concerns that need to be clarified in the post-marketing phase in each safety specification

The first step is to concretize concerns that need to be clarified in the post-marketing phase in each safety specification determined during the approval review process (i.e., what should be clarified, what information would be sufficient to judge the necessity and the content of solutions toward the concerns).

the content of solutions toward the concerns, and when to implement the solutions).	
Regarding "important identified risks," because a causal relationship between the drug and the adverse event has been well established, emphasis should be basically placed on risk minimization activities. However, when more detailed information regarding the common time of onset, the most appropriate treatment, the identification of risk factors, etc., is considered to be necessary, it may be better to clarify the purpose and consider conducting a study.	Regarding "important identified risks," because a causal relationship between the drug and the adverse event has been well established, identifying a risk factor for the adverse event can be an example of concerns that need to be clarified in the post-marketing phase.
Regarding "important potential risk," because a causal relationship between the drug and the adverse event remains unclear, a causal relationship of the risk would be a typical concern that needs to be clarified in the post-marketing phase.	Regarding "important potential risk," because a causal relationship between the drug and the adverse event remains unclear, a causal relationship of the risk would be a typical concern that needs to be clarified in the post-marketing phase.
Regarding "important missing information," one of the examples of concerns that need to be clarified in the post-marketing phase is the possibility that the incidence of known adverse drug reactions may differ between the population not included in pre-marketing clinical trials but expected to be treated with the drug in the post-marketing phase and other populations.	Regarding "important missing information," one of the examples of concerns that need to be clarified in the post-marketing phase is the possibility that the incidence of known adverse drug reactions may differ between the population not included in pre-marketing clinical trials but expected to be treated with the drug in the post-marketing phase and other populations.
Step 2) Determination of scientifically appropriate approach for each concern	**Step 2) Determination of a scientifically appropriate approach for each concern**
The second step is to determine the most scientifically appropriate approach for each concern specified in Step 1. Specifically, the best	The second step is to determine the most scientifically appropriate approach for each concern specified in Step 1. Specifically, the best

approach for each concern is considered by referring to the annex of the ICH E2E Guideline, etc. Depending on the characteristic of the concern, only passive surveillance, such as spontaneous reports and analysis based on literature, could be chosen as an approach, and post-marketing studies are not necessary for all concerns. <u>If a small sample size (overall study population or Japanese subpopulation) or a lack of information in some patient populations in a clinical trial is the only concern, it will not always serve as a rationale for conducting a survey or study even if such a concern is specified as "important missing information." A drug use-results survey has limited significance for the purpose of investigating the frequency of an important identified risk.</u>	approach for each concern is considered by referring to the annex of the ICH E2E Guideline, etc. Depending on the characteristic of the concern, only passive surveillance, such as spontaneous reports and analysis based on literature, could be chosen as an approach, and post-marketing studies are not necessary for all concerns.
When conducting post-marketing studies, it is necessary to formulate a research question for each concern, including population, intervention (exposure), comparison, outcome (safety specifications of interest), and timing. Then, study design, effect measure which will be eventually evaluated, and data source, etc. should be carefully considered on a basis of the research question.	When conducting post-marketing studies, it is necessary to formulate a research question for each concern, including population, intervention (exposure), comparison, outcome (safety specifications of interest), and timing. Then, study design, effect measure which will be eventually evaluated, and data source, etc. should be carefully considered on a basis of the research question.
(Omitted)	**Step 3) Confirmation of legal and regulatory framework where each approach to be compiled** Identify a regulatory framework where the approach determined in Step 2 must be compiled. Collection of spontaneous reports and literature etc. is conducted as "Routine Pharmacovigilance" in accordance with the Ministerial Ordinance on Good Vigilance Practice for Drugs, Quasi-drugs,

	Cosmetics, and Medical Devices (MHLW Ordinance No. 135, 2004; hereinafter referred to as "GVP"). On the other hand, a post-marketing study conducted as "Additional Pharmacovigilance" is subject to the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004; hereinafter referred to as "GPSP") in addition to the GVP. The "Additional pharmacovigilance" based on the GPSP are categorized into 3 types: "drug use-results survey (general drug use-results survey, specified drug use-results survey, drug use-results comparative survey)," "post-marketing database study," and "post-marketing clinical trial," which are generally recognized as follows: ● When information in routine clinical practice is collected directly in medical institutions, the study is categorized as a "drug use-results survey." ● When information is obtained from the medical information database, the study is categorized as a "post-marketing database study." ● When information that cannot be collected in routine clinical practice, such as an implementation of a specific examination, is obtained (i.e., when interventions are conducted), the study is categorized as a "post-marketing clinical trial." When a non-clinical study is conducted as "Additional Pharmacovigilance," the study is subject to the Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs (No. 21, Ministry of Health and Welfare, 1997) in addition to the GVP.

	In "additional pharmacovigilance" requiring the GPSP compliance, multiple types of studies (e.g., drug use-results survey and post-marketing database study) are basically not conducted simultaneously to address the same research question. If there are multiple research questions for a single product, an appropriate study will be identified for each approach of each research question. In that case, if the types of studies are the same in terms of the regulatory framework, planning one practical study for addressing those several research questions may be considered taking into consideration its feasibility, if necessary. (Newly established)
For new drugs subject to re-examination, it is not considered to be equally obligatory to conduct post-marketing study, etc. by laws and regulations. In addition, implementation of post-marketing study, etc. is not a prerequisite for granting a re-examination period.	
(Omitted)	**Step 4) Development of the study protocol** Develop a detailed plan (protocol) for each approach whose regulatory framework was identified in the previous step. In the plan development process, the details should be considered in the context of a research question, including eligibility criteria for the target population, exposure (drug use) definition, outcome definition, sample size, and statistical analysis methods etc., from the scientific point of view. The details of the protocol can be discussed in the PMDA consultation, such as "Consultation

	on post-marketing clinical trial plans" and "Consultation on pharmacoepidemiological study plans." When developing protocols for post-marketing database studies, please refer to the "Guidelines for the Conduct of Pharmacoepidemiological Studies in Drug Safety Assessment with Medical Information Databases" (PMDA, dated March 31, 2014) and the "Instructions for Post-marketing Database Study Protocols" (PMDA, dated January 23, 2018), etc. on the PMDA website, in addition to the notifications related to pharmacovigilance.

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Reference

PSEHB/PED Notification No. 0314-4
PSEHB/PSD Notification No. 0314-4
March 14, 2019
[Partial revision] July 18, 2024

To: Directors of Prefectural Health Departments (Bureaus)

Director of Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Director of Pharmaceutical Safety Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
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Procedures for Developing Post-marketing Study Plans for Drugs

With respect to the implementation of post-marketing studies of drugs, the Ministerial Ordinance for Partial Revision of the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 116, 2017) was recently enforced, and the positioning of “post-marketing database study” and “drug use-results comparative survey” has been newly clarified in the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004).

For post-marketing studies, it is important to conduct them efficiently and effectively by selecting the most scientifically appropriate approach according to their purposes. As shown in the attachment, the procedures for developing post-marketing study plans by marketing authorization holders of drugs have been formulated. Please cooperate in disseminating the following information to the relevant organizations under your jurisdiction.

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Post-marketing study plans consist of study plans for efficacy and pharmacovigilance plans, both of which will be planned when additional surveillance is necessary in the post-marketing phase. When a post-marketing study is conducted, it is important to clarify a research question based on the information obtained from pre-marketing clinical trials, the characteristics of target diseases and the drugs of interest, etc. and to conduct the study properly afterwards. At the same time, it should be noted that the purpose and the necessity of a post-marketing study should be fully considered to prevent the study from being conducted aimlessly. The research question here means a specific and clear aim of a study, including population, intervention (exposure), comparator, outcome (efficacy/safety specifications of interest), and timing. Based on the question, study design, effect measure which will be eventually evaluated, data source, etc. should be carefully considered.

Generally, efficacy data required for the marketing authorization (hereinafter referred to as "approval") are collected from pre-marketing clinical trials and a certain level of evaluation on efficacy is made at the time of approval. Therefore, if any specific concerns about efficacy are not raised during the approval review process or in the post-marketing phase, efficacy could be evaluated with means other than post-marketing studies (e.g., analysis based on literature). On the other hand, if a specific concern about efficacy arises during the approval review process or in the post-marketing phase, a post-marketing study should be implemented so that the concern can be scientifically verified.

Safety specifications are set based on the notification "Risk Management Plan Guidance" (No. 0411-1, by the Director of the Safety Division [SD], and No. 0411-2, by the Director of the Evaluation and Licensing Division [ELD], Pharmaceutical and Food Safety Bureau [PFSB], MHLW, dated April 11, 2012). With consideration for a scientific point of view and the current approval review process, development of pharmacovigilance plan can be divided into the following four steps (refer to the figure); 1) concretization of concerns that need to be clarified in the post-marketing phase in each safety specification, 2) determination of a scientifically appropriate approach for each concern, 3) confirmation of legal and regulatory framework where each approach to be compiled, and 4) development of the study protocol. In principle, an applicant should reach an agreement with the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") about Step 1-3 before the approval. The features and points to consider for each step are shown below. In addition, the following MHLW notifications (hereinafter referred to as "the notifications related to pharmacovigilance") should be referred to for consideration of them.

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- "Basic Principles on the Use of Medical Information Databases in Post-marketing Pharmacovigilance" (No. 0609-8, by the Director of the Pharmaceutical Evaluation Division, and No. 0609-4, by the Director of the SD, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 9, 2017)

If there is a specific safety concern and a research question can be formulated at the time of approval, a post-marketing study plan will be considered before approval (only its outline may be considered before approval, and a detailed study plan may be considered after approval.). In other cases, however, a post-marketing study plan, including its necessity, will be considered at an appropriate timing not before approval but in the post-marketing phase (when any new research question is developed e.g., when Early Post-marketing Phase Vigilance (EPPV) data are obtained or when a new concern arises and safety information that should be clarified in terms of post-marketing safety measures is obtained).

Early post-marketing phase vigilance (EPPV) is out of scope of this document because EPPV should be planned for each product according to the notification "Implementation Methods, etc. of Early Post-marketing Phase Vigilance for Prescription Drugs" (No. 0324001, by the Director of SD, PFSB, MHLW, dated March 24, 2006) and the administrative notice "Q & A on Early Post-marketing Phase Vigilance for Prescription Drugs" (SD, PFSB, MHLW, dated March 24, 2006).

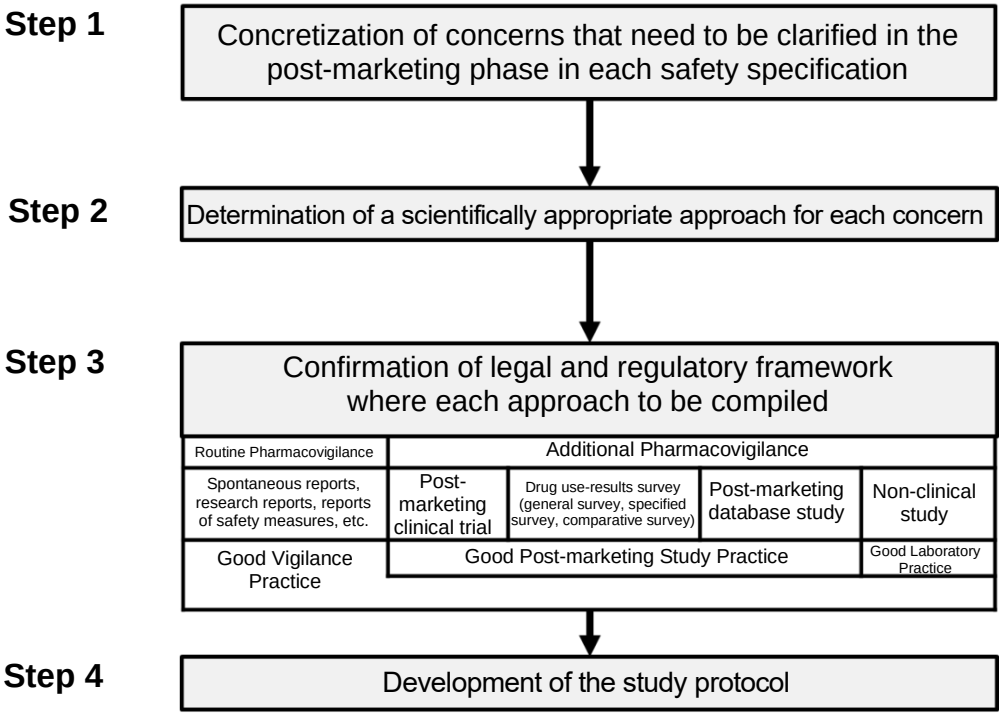

Figure. Overview of the development of pharmacovigilance planning

Step 1) Concretization of concerns that need to be clarified in the post-marketing phase in each safety specification

The first step is to concretize concerns that need to be clarified in the post-marketing phase in each safety specification determined based on the information obtained by the time of approval application (i.e., what should be clarified, what information would be sufficient to judge the necessity and the content of solutions toward the concerns, and when to implement the solutions).

Regarding “important identified risks,” because a causal relationship between the drug and the adverse event has been well established, emphasis should be basically placed on risk minimization activities. However, when more detailed information regarding the common time of onset, the most appropriate treatment, the identification of risk factors, etc., is considered to be necessary, it may be better to clarify the purpose and consider conducting a study.

Regarding “important potential risk,” because a causal relationship between the drug and the adverse event remains unclear, a causal relationship of the risk would be a typical concern that needs to be clarified in the post-marketing phase.

Regarding “important missing information,” one of the examples of concerns that need to be clarified in the post-marketing phase is the possibility that the incidence of known adverse drug reactions may differ between the population not included in pre-marketing clinical trials but expected to be treated with the drug in the post-marketing phase and other populations.

Step 2) Determination of scientifically appropriate approach for each concern

The second step is to determine the most scientifically appropriate approach for each concern specified in Step 1. Specifically, the best approach for each concern is considered by referring to the annex of the ICH E2E Guideline, etc. Depending on the characteristic of the concern, only passive surveillance, such as spontaneous reports and analysis based on literature, could be chosen as an approach, and post-marketing studies are not necessary for all concerns. If a small sample size (overall study population or Japanese subpopulation) or a lack of information in some patient populations in a clinical trial is the only concern, it will not always serve as a rationale for conducting a survey or study even if such a concern is specified as "important missing information." A drug use-results survey has limited significance for the purpose of investigating the frequency of an important identified risk.

When conducting post-marketing studies, it is necessary to formulate a research question for each concern, including population, intervention (exposure), comparison, outcome (safety specifications of interest), and timing. Then, study design, effect measure which will be eventually evaluated, and data source, etc. should be carefully considered on a basis of the research question.

Step 3) Confirmation of legal and regulatory framework where each approach to be compiled

Identify a regulatory framework where the approach determined in Step 2 must be compiled. Collection of spontaneous reports and literature etc. is conducted as "Routine Pharmacovigilance" in accordance with the Ministerial Ordinance on Good Vigilance Practice for Drugs, Quasi-drugs, Cosmetics, and Medical Devices (MHLW Ordinance No. 135, 2004; hereinafter referred to as "GVP"). On the other hand, a post-marketing study conducted as "Additional Pharmacovigilance" is subject to the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004; hereinafter referred to as "GPSP") in addition to the GVP. The "Additional pharmacovigilance" based on the GPSP are categorized into 3 types: "drug use-results survey (general drug use-results survey, specified drug use-results survey, drug use-results comparative survey)," "post-marketing database study," and "post-marketing clinical trial," which are generally recognized as follows:

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- When information that cannot be collected in routine clinical practice, such as an implementation of a specific examination, is obtained (i.e., when interventions are conducted), the study is categorized as a "post-marketing clinical trial."

When a non-clinical study is conducted as "Additional Pharmacovigilance," the study is subject to the Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs (No. 21, Ministry of Health and Welfare, 1997) in addition to the GVP.

In "additional pharmacovigilance" requiring the GPSP compliance, multiple types of studies (e.g., drug use-results survey and post-marketing database study) are basically not conducted simultaneously to address the same research question.

If there are multiple research questions for a single product, an appropriate study will be identified for each approach of each research question. In that case, if the types of studies are the same in terms of the regulatory framework, planning one practical study for addressing those several research questions may be considered taking into consideration its feasibility, if necessary.

For new drugs subject to re-examination, it is not considered to be equally obligatory to conduct post-marketing study, etc. by laws and regulations. In addition, implementation of post-marketing study, etc. is not a prerequisite for granting a re-examination period.

Step 4) Development of the study protocol

Develop a detailed plan (protocol) for each approach whose regulatory framework was identified in the previous step. In the plan development process, the details should be considered in the context of a research question, including eligibility criteria for the target population, exposure (drug use) definition, outcome definition, sample size, and statistical analysis methods etc., from the scientific point of view. The details of the protocol can be discussed in the PMDA consultation, such as "Consultation on post-marketing clinical trial plans" and "Consultation on pharmacoepidemiological study plans."

When developing protocols for post-marketing database studies, please refer to the "Guidelines for the Conduct of Pharmacoepidemiological Studies in Drug Safety Assessment with Medical Information Databases" (PMDA, dated March 31, 2014) and the "Instructions for Post-marketing Database Study Protocols" (PMDA, dated January 23, 2018), etc. on the PMDA website, in addition to the notifications related to pharmacovigilance.