January 23, 2018

Procedures for Developing Post-marketing Study Plan

Pharmaceuticals and Medical Devices Agency

The revised "Ministerial Ordinance on Good Post-marketing Study Practice for Drugs" (No. 171, Ministry of Health, Labour and Welfare [MHLW], dated December 20, 2004) (hereinafter referred to as "*GPSP*") will be implemented in April 2018. It clearly defines "Post-marketing database study", marketing authorization holders requiring to conduct more efficient and effective studies after drug marketing with more suitable and scientific methods than before. Therefore, basic policy for consideration to develop a Post-marketing study[1] plan is hereby released.

A Post-marketing study plan consists of studies for effectiveness and a pharmacovigilance plan when additional studies are required after launch. When a Post-marketing study is conducted, it is important to conduct a study properly corresponding to a clarified research question, which is based on the information of pre-marketing clinical trials and the characteristics of target diseases and concerned products. At the same time, it should be noted that a marketing authorization holder and the Pharmaceuticals and Medical Devices Agency (PMDA) shall take care to avoid conducting a study whose purpose is unclear. The research question here means a specific and clear aim of a study, including population, intervention (exposure), comparator, outcome, and timing. Based on the question, study design, effect measurement (i.e., risk ratio), data source, etc. should be carefully considered.

Generally, efficacy data required for 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

[1] "Post-marketing study" is conducted for re-examination submission based on regulatory standard such as the *GPSP* (i.e., "Post-marketing database study", "Post-marketing clinical trial", "Post-marketing observational study with primary data collection" etc) in this document.

concerns about efficacy are raised during the approval review process or after marketing, efficacy could be monitored in means other than Post-marketing studies (e.g., analysis based on literatures). On the other hand, if a specific concern about efficacy arises during the approval review process or after marketing, a Post-marketing study should be implemented so that the specific concern can be scientifically clarified.

Safety specification is 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). When considering scientific point of view and the approval review process, development of pharmacovigilance plan consists of the following four steps (refer to the figure); 1) concretizing a concern that need to be clarified in the post-marketing setting per each safety issue in safety specification, 2) determination of scientifically appropriate approach per each concern, 3) ensuring applicable regulatory framework for each approach, and 4) development of a detailed study protocol per each research question. In principle, an applicant should reach an agreement with PMDA about Step 1-3 for all safety issues in safety specification 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 for consideration of them.

- ICH E2E Guideline “Pharmacovigilance planning” (No. 0916001, by the Director of ELD, and No. 0916001, by the Director of SD, PFSB, MHLW, dated September 16, 2005)
- “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 SD, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 9, 2017)

Early Post-marketing Phase Vigilance (EPPV) is out of scope of this document because EPPV should be planned per each product, not per safety issue in safety specification, 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).

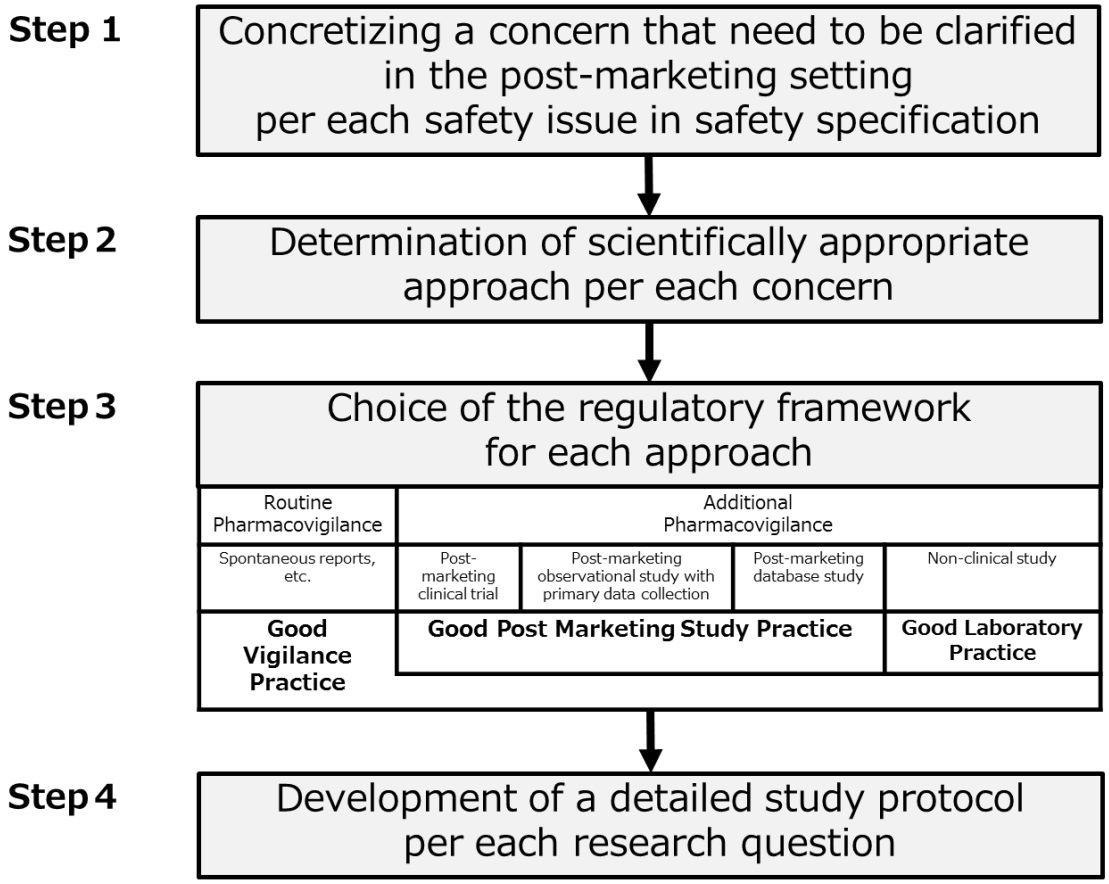

Figure. How to develop pharmacovigilance planning

Step 1. Concretizing a concern that need to be clarified in the post-marketing setting per each safety issue in safety specification

The first step is to concretize a concern that needs to be clarified in post-marketing per each safety issue in safety specification determined during the approval review process (i.e., what should be clarified, what information would be sufficient for safety assessment and for taking safety-related regulatory actions).

- Regarding “important identified risks”, since a causality between the drug and the adverse event has been clarified, identifying a risk factor for the adverse event could be an example of concerns that need to be clarified in post-marketing.
- Regarding “important potential risk”, because a causality between the drug and the adverse event has not been clarified, a causality of the risk would be a typical concern that need to be clarified in post-marketing.
- Regarding “important missing information”, an example of concerns that need to be clarified in post-marketing 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 after marketing and other populations.

Step 2. Determination of scientifically appropriate approach per each concern

The second step is to determine the most scientifically appropriate approach per each concern specified in Step 1. Specifically, the best approach per 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 literatures, 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, and timing. Then, appropriate study design, effect measure, and data source, etc. should be examined on a basis of the research question.

Step 3. Choice of the regulatory framework for each approach

Identify regulatory framework suitable for the approach determined in Step 2. A collection of adverse reaction reports and literatures is conducted as “Routine Pharmacovigilance” according to the “Ministerial Ordinance on Good Vigilance Practice for Drugs, Quasi-drugs, Cosmetics, and Medical Devices” (No. 135, MHLW, dated September 22, 2004) (hereinafter referred to as “*GVP*”). On the other hand, Post-marketing study conducted as “Additional Pharmacovigilance” is subject to the *GPSP* in addition to the *GVP*. The studies based on the *GPSP* are categorized into 3 types: “Post-

marketing clinical trial", "Post-marketing observational study with primary data collection[2] (single cohort study, specific cohort study, comparative cohort study)", and "Post-marketing database study", which are generally recognized as follows:

- When information in routine clinical practice is obtained directly from medical institutions, the study is categorized as a "Post-marketing observational study with primary data collection".
- When information is acquired from the medical information database, the study is categorized as a "Post-marketing database study".
- When information that cannot be obtained in routine clinical practice is acquired (e.g., when interventions such as a specific examination are conducted), the study is categorized as a "Post-marketing clinical trial".

When a non-clinical study is conducted as "Additional Pharmacovigilance", the "Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs" (No. 21, Ministry of Health and Welfare, dated March 26, 1997) is applied in addition to the *GVP*.

In principle, multiple studies as "Additional Pharmacovigilance" requiring the *GPSP* compliance (e.g., Post-marketing observational study with primary data collection and Post-marketing database study) are not conducted in parallel for the same research question.

In case that there are plural research questions for a single product, a regulatory framework is identified for the approach of each research question. However, if necessary, it may be a case to conduct one practical study addressing those multiple research questions with taking into consideration its feasibility.

Step 4. Development of a detailed study protocol per each research question

Develop a detailed plan (protocol) for the research question identified by the previous step as an "Additional Pharmacovigilance". In the process, the details should be

[2] "Post-marketing observational study with primary data collection" is "Shiyou seiseki chousa" in Japanese, which is occasionally translated into "Drug use results survey" in some documents.

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: “Consultation on post-marketing clinical trial plans” and “Consultation on pharmacoepidemiological study plans”, etc.

When developing the 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.