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

Basic Principles on the Use of Medical Information Databases in Post-marketing Pharmacovigilance

The method of post-marketing pharmacovigilance has been shown in the “Pharmacovigilance Planning” (PFSB/ELD Notification No. 0916001 and PFSB/SD Notification No. 0916001, dated September 16, 2005, by the Director of Evaluation and Licensing Division and the Director of Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (hereinafter referred to as MHLW)) and other notifications.

Now, the full-scale operation of MID-NET, a medical information database system under development by the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as PMDA), is scheduled to start, and an environment is being established to allow the medical information databases to be used for pharmacovigilance. Taking this into account, the basic principles when the medical information databases are used in post-marketing pharmacovigilance by pharmaceutical marketing authorization holders have been made as below. Please understand the principles provided herein, and inform the relevant organizations under your jurisdiction.

The characteristics and points to consider of major pharmacovigilance methods,

including the use of the medical information databases, are also provided as shown in the Appendix for your reference coupled with the principles.

Notice

1. Scope of application

This notification applies mainly when post-marketing pharmacovigilance activities are conducted for new drugs using the medical information databases.

In this notification, “medical information databases” refer to a database systematically accumulating electronic medical information such as hospital information system data (electronic medical record data, Diagnosis Procedure Combination [DPC] data, etc.), claims for medical fees and dispensing fees (e.g. receipt data of health insurance associations), and disease registry data.

2. Planning and conducting of a study using the medical information databases

When conducting the post-marketing pharmacovigilance activities, specific issues (research questions) should be established in advance, regardless of the methods of the study to be selected, in order to obtain scientific evidence leading to the implementation of effective safety measures. On that basis, appropriate study methods that can address the established issues must be sufficiently examined.

Based on its purpose, the implementation of the study using the medical information databases should be considered, when the study is expected to be appropriate with expedition. For example, a study using the medical information databases may be appropriate in the following cases:

- When an event of concern is found in the information of adverse drug reaction reporting, the frequency and trend of the event, or factors related to it in a specific population are explored;
- When the actual status of prescription is studied in order to consider the method and contents for providing information on proper use;
- When it is considered inappropriate to conduct a study in which the marketing authorization holders and other entities collect data from medical institutions by themselves, taking into account the number of cases and study period required for evaluation;
- When a control group is set up to evaluate, for example, whether an adverse event is associated with a specific drug, concerning the events that can occur

regardless of the use of drugs;

- When conducting a quantitative or over-time evaluation on the effects of the implementation of safety measures, such as whether risks have been reduced as a result of implementation of risk minimization activities, compared to before implementation of the activities.

3. Selection of medical information databases

For selection of medical information databases, it should be confirmed that the reliability of the data is ensured, and sufficient examination should be performed in advance on the characteristics of the database such as the owner of the database, period of the accumulated data, sample size and characteristics of the population to be studied, traceability, range of drugs that can be studied, adverse events that can be studied, and procedures for obtaining data.

4. Development of study plan using medical information databases

(1) Based on the “Guideline for the Conduct of Pharmaco-epidemiological Studies in Drug Safety Assessment with Medical Information Database” (dated March 31, 2014, by the PMDA), the characteristics of the data elements to be used for evaluation should be carefully examined, and then the study plan and its statistical method should also be examined sufficiently in advance. In particular, it is important to make the plan after fully understanding the clinical significance of the data elements, method of operation on the data elements in medical practice, etc.

(2) When a feasibility study, tentative analysis, etc. are conducted to examine a database to be used, study design, or analysis method, etc. prior to the development of the study plan, sufficient attention should be paid lest the developed survey plan should be intentionally advantageous to the drug to be studied.

(3) In principle, a study with a control group should be conducted so that sufficient scientific evidence leading to the implementation of effective safety measures can be obtained. When an existing drug is set up as a control, an appropriate drug should be selected from scientific and clinical viewpoints, also based on the treatment guideline for the indication, the mechanism of action of the drug, etc.

(4) When a study is conducted using overseas medical information databases, the justification, etc. for extrapolating the study results to the Japanese population should be examined additionally.

5. Other

When pharmacovigilance activities and risk minimization activities are added, changed, or terminated based on the results of the study using the medical information databases, the decision should be made after carefully evaluating the clinical significance of the study results and comprehensively evaluating it together with other information.

(Reference)

Pharmaceuticals and Medical Devices Agency website

- Advanced Database Analysis Method Project

  URL: https://www.pmda.go.jp/safety/surveillance-analysis/0032.html (Only in Japanese)

- Guideline for the Conduct of Pharmaco-epidemiological Studies in Drug Safety Assessment with Medical Information Database

  URL: https://www.pmda.go.jp/files/000147250.pdf (Only in Japanese)

  English version is also available

  URL:https://www.pmda.go.jp/files/000240945.pdf

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Appendix

Characteristics and points to consider of major pharmacovigilance methods

1. Study based on spontaneous adverse drug reaction reporting from medical institutions, etc.

<Characteristics>

- It is possible to obtain detailed information on the temporal relationship between the use of the drug and the onset of the adverse drug reaction, course of the adverse drug reaction, and laboratory findings.
- Less frequent adverse drug reactions that could not be detected in clinical trials or adverse drug reactions in patient populations not included in clinical trials may be detected.
- When early post-marketing phase vigilance is conducted, the adverse drug reaction reporting is promoted for 6 months after the start of marketing. Thus, information on adverse drug reactions in the early post-marketing phase can be collected promptly.

<Points to consider>

- Since only the information on patients who developed adverse drug reactions is accumulated, the total number of patients using the drug is unknown, the frequency cannot be obtained, and therefore there is a limit to conducting scientific evaluation.
- In a disease area with a higher frequency of a specific adverse event, regardless of the presence or absence of the causal relationship with a drug, it is difficult to assess the causal relationship between the event and the use of the drug.
- It is difficult to quantitatively evaluate the relative risk compared to the control group.
- If the assessment on the causal relationship based on the temporal relationship between the use of the drug and the onset of the adverse event is difficult (e.g., carcinogenicity or onset of dyslipidaemia due to long-term use), the event may not be collected as an adverse drug reaction report.

- Since it depends on the reporter's initiative whether or not the event is judged to be an adverse drug reaction or whether or not it should be reported, sufficient attention should be paid to reporting bias and other factors when evaluating/interpreting the accumulated results.
- The characteristics of a patient who uses a drug, the amount of the drug used, etc. are different depending on the drug, and thus the number of adverse drug reaction reports does not necessarily reflect the frequency of adverse events for individual drugs.

2. Drug use-results survey

<Characteristics>

- Elements to be collected can be set according to the purpose of the survey, and medical information can be collected from multiple medical institutions by a unified method.
- If appropriate sampling is performed, the frequency of adverse events can be examined.
- If there is a control group, the relative risk can be estimated by adjusting the effects of background factors and other effects.
- For orphan drugs, etc., for which the sample size evaluated is extremely limited at the time of marketing approval, this may be useful as a method to compensate promptly for the lack of safety information.

<Points to consider>

- Since the sample size that can be actually surveyed is limited, it may be difficult to scientifically assess the causal relationship between adverse events with very low frequency and the use of the drug.
- Considerations needs to be given to whether the obtained results can be generalized or not based on the selection of medical institutions to be surveyed, timing (e.g., early post-marketing phase) for selection of cases and implementation of the survey, etc.
- Cooperation of medical institutions is essential to collect medical information, and the timely collection of medical information entails a heavy human, financial, and labor burden on marketing authorization holders and medical institutions.

3. Study using medical information databases

<Characteristics>

- It is easy to conduct a study targeting a large number of cases or a study in which a group of an existing other drug or a non-treatment group, etc. are set up as a control.
- The total number of patients who uses a specific drug among those registered in the targeted databases can be obtained, and accordingly, also the frequency of adverse events, etc. can be calculated.
- If sufficient data necessary for the study have been accumulated, tabulation and safety assessment can be performed in a short period after the start of the study.
- Since the information accumulated previously in the databases is used, it is not necessary to fill out the study form at the time of implementation of the study, and consequently, the burden on the medical practice is light, and the human/financial burden is generally light also regarding social aspects.
- It may be possible to evaluate the natural course, survival time, etc. by using a database in which data have been accumulated over a long period of time.
- It may be possible to conduct a study using information as a historical control for pre-marketing approval or a study to evaluate changes in the situation before and after social interventions, such as implementation of safety measures.

<Points to consider>

- The available study elements vary by database and may not be comprehensive for the purpose of the study.
- Consideration needs to be given to whether the results obtained in the study can be generalized or not, such as whether the database used for the study includes a population that is representative of the patient populations to be studied.
- The outcome to be assessed needs to be clearly defined before the start of the study, and thus this study is not suitable to detect events that cannot be defined.
- When the method for collecting each element accumulated in the database is checked and any operational issue is found, it may be necessary to individually examine the reliability of data, and other properties.
- When conducting a study, the outcome definition should be carefully examined in consideration of the clinical significance, and it needs to be confirmed in advance that the outcome to be assessed can be identified with high accuracy from the data based on the results of validation studies including the existing

studies. When using an outcome definition with unknown accuracy, validation needs to be performed in advance.

- In general, there is a certain time lag before the latest information is accumulated in the database, and therefore, the contents and characteristics of data to be used need to be understood before analysis.
- When performing the analysis, it is necessary to sufficiently examine the study protocol, analysis method, etc. in advance lest the analysis should be an arbitrary post-hoc analysis.

4. Post-marketing clinical studies

<Characteristics>

- By setting the study design and endpoints according to the purpose, enough necessary information can be obtained.
- Measures such as randomization and blinding can be taken, and by conducting a study with an appropriate study protocol in accordance with the GCP, high-quality data can be collected and issues can be verified in order to scientifically evaluate the safety and efficacy.
- By setting an appropriate control group such as a standard therapy for the indication of the drug to be studied, the clinical positioning of the drug to be studied can be clarified.
- By setting the sample size that enables scientific verification, safety issues that are difficult in observational studies can be verified in interventional studies primary focusing on the safety.

<Points to consider>

- Cooperation of medical institutions and subjects is essential, and it may take a long time to secure the number of cases in accordance with the purpose.
- To conduct the study, a much heavier human and financial burden and labor burden on medical institutions are required compared to non-interventional studies.
- In general, subjects enrolled in clinical studies are part of patients targeted in clinical practice, and treatments are managed based on strict standards. Therefore, it needs to be carefully examined whether generalization is possible when interpreting the results.

5. Studies based on research literature

<Characteristics>

- If the research is conducted based on an appropriate plan, safety information based on scientific evidence and information supporting the benefit-risk evaluation may be efficiently collected with a light human and financial burden.

<Points to consider>

- The appropriateness of the literature database and search formula need to be explained based on the evidence, and the information should be reviewed over time as it is updated constantly.
- To appropriately evaluate the results obtained in the literature, the purpose, characteristics and limitations of the study design, etc. need to be carefully examined.