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To: Head of organizations listed in the separate notes

Pharmaceuticals and Medical Devices Agency
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Development of Basic Principles in Conducting a Validation of Outcome Definitions used in Post-marketing Database Studies

In the “Ministerial Ordinance for Partial Revision of the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 116, 2017)” enforced on April 1, 2018, post-marketing database studies (hereinafter referred to as "post-marketing DB studies"), by utilizing medical information databases provided by medical information database holders, were explicitly specified as one of the post-marketing surveillances conducted by marketing authorization holders, etc. to prepare application materials for re-examination and re-evaluation.

When conducting post-marketing DB studies, it is important to carefully consider outcome definitions and, if necessary, to validate the outcome definitions. Therefore, the basic principles in conducting a validation of outcome definitions used in post-marketing DB studies were developed as shown in the attachment. Please understand the contents, and notify your organization members, etc. to that effect.

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(Separate notes)

The federation of Pharmaceutical Manufacturer's Associations of Japan

Japan Pharmaceutical Manufacturers Association

Japan-Based Executive Committee of the Pharmaceutical Research and Manufacturers of America

European Federation of Pharmaceutical Industries and Associations

Japanese Society for Pharmacoepidemiology

Society for Clinical Epidemiology

Japan Epidemiological Association

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Basic Principles in Conducting a Validation of Outcome Definitions used in Post-marketing Database Studies

July 31, 2020
Pharmaceuticals and Medical Devices Agency

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Contents

1. Background and purposes of this document 3
2. Scope of this document....3
3. Importance of validation of outcome definitions 4
4. Standard method for validation of outcome definitions 5
5. Specific points to consider in a validation protocol 6
5-1. Clarification of the outcomes of interest....7
5-2. Organizing characteristics of medical information databases and preparing outcome definitions 7
5-3. Definition of index date....9
5-4. Consider the setting of study population....9
5-5. Selection of validation facilities 10
5-6. Preparation of code lists and programs, etc. for data extraction 11
5-7. Assessment of true cases....12
5-7-1. How to assess true cases 12
5-7-2. Person assessing true cases in a medical record review 13
5-8. Evaluation of outcome definitions....13
5-8-1. Indicators to be used in validation of outcome definitions....13
5-8-2. Sensitivity calculation method 14
5-8-3. Number of the target cases at the time of a medical record review 15
5-9. Determination of appropriate outcome definitions....15
6. Other points to consider....16
6-1. Publication of validation results....16
6-2. Re-implementation of validation....16
7. Definition of term 17

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1. Background and purposes of this document

The "Risk Management Plan Guidance (PFSB/SD Notification No. 0411-1, PFSB/ELD Notification No. 0411-2)" issued on April 11, 2012 describes the availability of medical information databases in pharmacovigilance activities. Also, in the “Ministerial Ordinance for Partial Revision of the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 116, 2017)” enforced on April 1, 2018, post-marketing database studies (hereinafter referred to as "post-marketing DB studies"), by utilizing medical information databases provided by medical information database holders, were explicitly specified as one of the post-marketing surveillances conducted by marketing authorization holders, etc. to prepare application materials for re-examination and re-evaluation. Points to consider when using medical information databases in post-marketing pharmacovigilance activities are presented in the "Basic Principles on the Use of Medical Information Databases in Post-marketing Pharmacovigilance (PSEHB/PED Notification No. 0609-8 and PSEHB/PSD Notification No. 0609-4 dated June 9, 2017).” When post-marketing DB studies are conducted, outcome definitions and whether the appropriateness of the outcome definitions is validated (hereinafter referred to as "validation") as necessary should be carefully considered.

This document describes the basic principles in conducting a validation of outcome definitions used in post-marketing DB studies for the purpose of promoting smooth implementation of validation. If there is a rational basis reflecting academic progress, etc., it is not necessarily required to adhere to methods shown in this document.

2. Scope of this document

This document is applicable to post-marketing DB studies for re-examination and re-evaluation applications, in which validation is performed for outcome definitions used in a study[1)] conducted to serve as the main basis for concrete safety measures, etc.

For definitions of terms used in this document, see Chapter 7.

[1] It refers to a study, etc. to strengthen or mitigate a level of attention calling in a package insert (excluding addition of new items) or to examine matters related to studies or re-evaluation performed to make the details of attention calling more specific because information required to take safety measures is insufficient, although there are specific concerns about safety, etc.

3. Importance of validation of outcome definitions

When post-marketing DB studies are conducted, effect indicators, such as incidence proportion, incidence rate and relative risk, are calculated for the target outcomes to evaluate the safety of drugs. Although it varies depending on the study purpose, it is important to accurately identify the onset of outcomes in order to appropriately calculate the effect indicators. As in the case of outcomes that can be defined based only on laboratory test results, if the onset of an outcome can be objectively identified based only on information recorded in medical information databases, the information can be directly used, and validation is not necessary. However, even for such outcomes, it is important to appropriately consider outcome definitions after fully understanding the actual situation of medical practices (e.g., methods for the diagnosis of outcomes such as specimen tests and physiological tests, etc., drug therapies, and therapeutic interventions, such as surgeries). Points to consider for identifying the onset of outcomes based on laboratory test results are provided in the appendix for reference.

On the other hand, if the onset of outcomes cannot be objectively identified based on information contained in medical information databases, it is common to prepare outcome definitions combining medical information (e.g., assignment of disease names, prescription of drugs, and implementation/results of laboratory tests) recorded in the databases and to identify cases meeting the outcome definitions as true cases. It is important to understand how well these prepared outcome definitions can identify actually true cases. For example, when the occurrence of an outcome is assumed only by a disease name recorded in medical information databases, it may include cases in which an outcome has not actually occurred. Therefore, in order to appropriately implement a safety evaluation of drugs and safety measures, etc., it is necessary to preliminarily examine the appropriateness of outcome definitions and to clarify characteristics, etc. of populations identified when the outcome definitions are used.

As described above, it is important to examine the appropriateness of outcome definitions in evaluating results of post-marketing DB studies. Therefore, it is desirable to consult with the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") in advance about a validation protocol, including the necessity of validation, after consideration of these with reference to this document.

In addition, cooperation of medical institutions and medical information

database holders is essential for implementation of validation; therefore, persons (pharmaceutical companies, etc.), who plan/implement validation, should fully explain the importance and necessity, etc. of validation to medical institutions and medical information database holders.

4. Standard method for validation of outcome definitions

The standard method for validation of outcome definitions (figure below) is assumed to be consisting of 1) Clarification of the outcomes of interest, 2) Organizing characteristics of medical information databases and preparing outcome definitions, 3) Definition of index date, 4) Consider the setting of study population, 5) Selection of facilities where validation is performed (hereinafter referred to as "validation facilities"), 6) Preparation of code lists and programs, etc. for data extraction, 7) Assessment of true cases, 8) Evaluation of outcome definitions, and 9) Determination of appropriate outcome definitions. These do not necessarily specify that they should be performed in the same order because it may be better to perform them in parallel or in a rearranged order. As a result of evaluation of outcome definitions, if a sufficient positive predictive value (hereinafter referred to as "PPV") or sensitivity is not obtained, it is necessary to reconsider the outcome definitions or to consider the appropriateness of using the outcome definition in post-marketing DB studies.

In addition, when selecting outcome definitions to be used in post-marketing DB studies, validation results should also be sufficiently considered. Therefore, validation of the outcome definitions should be performed before the start of post-marketing DB studies in principle.

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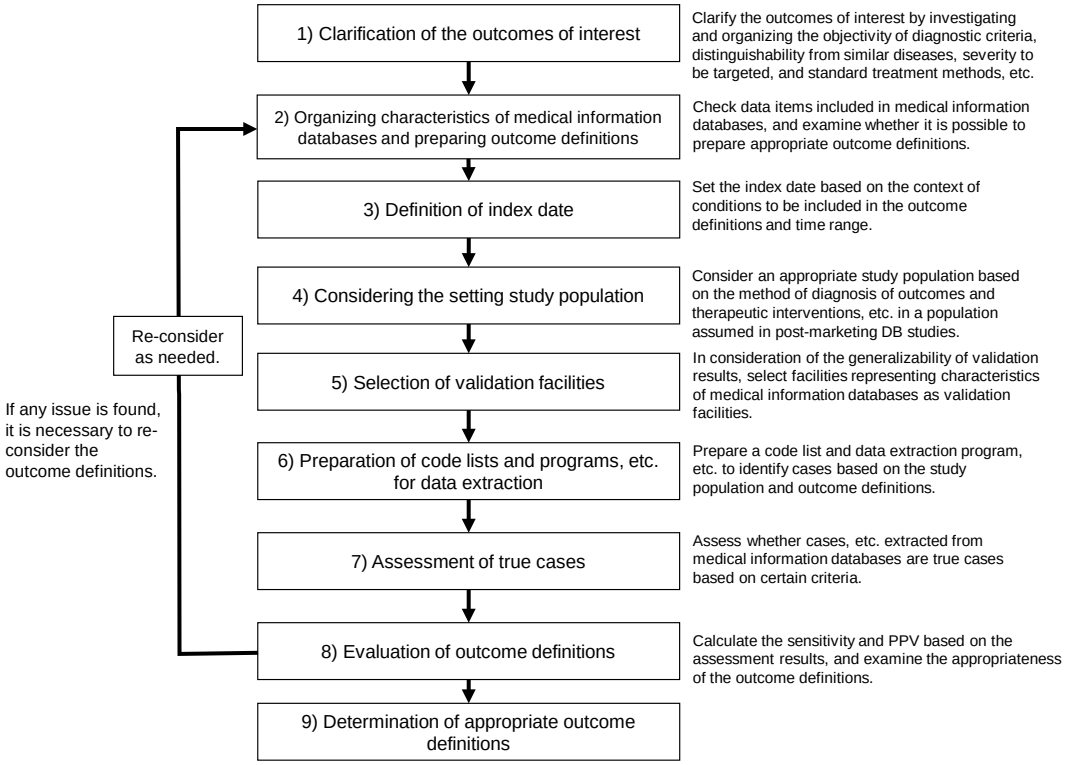

Figure. Standard method for validation of outcome definitions

5. Specific points to consider in a validation protocol

When performing validation of outcome definitions, it is important to plan a protocol so that matters to be considered from the pharmacoepidemiological viewpoint can be sufficiently examined after accurately understanding the situation in the actual clinical practice. In order to do that, those (pharmaceutical companies, etc.), who plan and implement validation, should fully consider the matters and the protocol. For example, it is desirable to consider them with the advice from experts having the following expertise from the planning stage.

- Physicians who are well-experienced in clinical practice and familiar with diagnosis and treatment, etc. regarding the following points at medical institutions included, or may be included, in medical information databases to be used in post-marketing DB studies
  - Indications of drugs to be investigated in post-marketing DB studies
  - Outcomes subject to post-marketing DB studies
- Experts who specialize in medical information and are familiar with validation of outcome definitions

- Experts who specialize in pharmacoepidemiology or biostatistics and are familiar with validation of outcome definitions
- Health Information Managers who are familiar with recording and processing of medical information, such as electronic health insurance claims data

In addition, matters to be particularly noted in each process are described in Sections 5-1 to 5-9. These matters should be carefully considered, and a handling method, etc. should be clearly described in a validation protocol.

5-1. Clarification of the outcomes of interest

When post-marketing DB studies are planned for safety specifications listed in a risk management plan, outcome definitions will be prepared for the outcomes of interest. In order to appropriately prepare outcome definitions by combining a lot of medical information, it is necessary to clarify them from a clinical point of view including severity, in light of not only classification of diseases, such as pneumonia and cardiac failure, but also matters of concern to be investigated and to consider what events are to be specifically examined in the post-marketing DB study. For example, the conditions for medical information to be included in outcome definitions vary depending on whether only severe cases needing hospitalization or surgery are included or whether mild cases are also included even when they are the same diseases. Taking into account the severity and symptoms, etc. at the time of onset, it is necessary to clarify outcomes subject to post-marketing DB studies before preparing a validation protocol and to reach an agreement with PMDA in advance.

It is also necessary to consider the necessity of preparing more than one independent outcome definition, in order to appropriately identify the onset of outcomes subject to post-marketing DB studies. For example, when examining cerebral stroke in the study, instead of preparing a single outcome definition to identify cerebral stroke, the necessity to divide cerebral stroke into several diseases, such as cerebral infarction and cerebral hemorrhage, from a clinical point of view and to prepare an independent outcome definition for each may be considered.

5-2. Organizing characteristics of medical information databases and preparing outcome definitions

In order to prepare appropriate outcome definitions, it is first necessary to

accurately understand characteristics of a medical information database and to organize data items available in the medical information database and contents, etc. contained in the items. Then, based on the consideration in Section 5-1, outcome definitions that are assumed to most appropriately identify the onset of the target outcomes based on the data items available in the database are prepared. In general, medical practices, etc. that may be performed at the onset of the outcomes are checked, and then outcomes are defined by combining multiple conditions, such as assignment of related disease names, prescription of drugs, implementation/results of laboratory tests, and so forth. In addition, when preparing outcome definitions, it is necessary to consider and clarify the following points, etc.

- Sources and data items of medical information to be used for the definitions: For example, regarding the disease names, it should be considered which medical information sources must be used because there are various sources of information (e.g., health insurance claims data, DPC data, and electronic medical record data) and data items (e.g., primary disease name and disease name on which the most medical resources are used etc. are available in DPC data).
- Temporal relationship of multiple conditions in the definitions: For example, when preparing an outcome definition by combining two conditions, such as assignment of disease names and prescription of drugs, it must be considered whether only the prescription of drugs on the same day as the date of assignment of disease names is focused or whether the prescription of drugs within a certain period including the date of assignment of disease names is focused as the outcome definitions.

In general, in order to make it possible to appropriately select outcome definitions to be used in post-marketing DB studies from among multiple candidates, it is recommended to prepare several to a dozen of the outcome definitions, not one, for the outcomes of interest and to calculate indicators, such as PPV and sensitivity, for each outcome definition. For each outcome definition prepared, it is desirable to confirm the number of patients, etc. meeting each condition or outcome definition at validation facilities as much as possible at the stage of the preparation of the outcome definition from the viewpoint of feasibility of validation ensuring a sufficient number of cases.

5-3. Definition of index date

The index date for validation of outcome definitions is the essential information of the date, which is treated as a reference point of the temporal relationship of conditions (e.g., date of onset of outcome or date of cohort entry) to be included in the outcome definitions, a starting point of time range, or a starting point of the target period for a medical record review. Also, because the index date may be defined as the onset date of an outcome identified by using the outcome definition in post-marketing DB studies, it is necessary to pay attention to this point and to carefully consider it after understanding characteristics, etc. of data.

If a patient is expected to have multiple index dates due to recurrent events, etc., it is necessary to determine whether only the initial index date is subject to validation or whether all index dates are subject to validation. Detailed methods of handling should be considered based on characteristics of diseases as outcomes (acute or chronic diseases, etc.), the original source of the date information used as the index date, method of the statistical analysis in post-marketing DB studies using outcome definitions, and so forth.

5-4. Consider the setting of study population

Regarding study populations for validation of outcome definitions, detailed inclusion criteria, etc. will be determined based on a study population assumed in post-marketing DB studies and setting of the study population needs to be carefully considered.

In general, it is efficient to conduct validation in the widest possible patient population in order to minimize the efforts of validation for the same outcome and to use outcome definitions, whose appropriateness has been validated, as broadly as possible. For this reason, in setting a study population, it is recommended to examine each outcome whether or not medical practices, etc. for the outcomes of interest differ according to the underlying diseases. After that , it is also recommended to consider setting a study population, a maximum group of people with similar medical practices, etc. and having no difference in conditions that make up the outcome definitions. For example, when an adverse event associated with drug administration for Disease A is examined, if medical practices, etc. that may be performed are not different between patients with Disease A who experience the adverse event and patients with Diseases B who experience the same adverse event, the possibility may be considered that patients with not only Disease A but also Disease B are included in the target

patients for validation of outcome definitions.

On the other hand, if a study population in post-marketing DB studies cannot be considered to be the same as a study population in validation from the viewpoint of patient background because diagnostic methods of outcomes and therapeutic interventions are specific, etc. in the study population in the post-marketing DB studies, additional considerations may be needed, such as conducting validation by limiting the target population to the study population in the post-marketing DB studies, even if outcome definitions are the same.

It is useful to conduct subgroup analyses focusing on major factors, such as differences in underlying diseases and severity, in a study population and to examine the scope of populations in which outcome definitions prepared can be applied.

When conducting post-marketing DB studies, it is necessary to carefully consider whether outcome definitions prepared are applicable to a study population of post-marketing DB studies based on the study population and results of validation.

5-5. Selection of validation facilities

Ideally, validation of outcome definitions should be performed at all medical institutions included in medical information databases to be used in post-marketing DB studies. However, because it is unachievable to perform validation at all medical institutions in most cases, it is necessary to select validation facilities, and sometimes it is assumed to be performed at medical institutions that are not included in the medical information databases. For this reason, multiple validation facilities should be selected in principle so that generalizability, etc. to the entire medical information databases used can also be examined.

When selecting validation facilities, characteristics of medical institutions included in the medical information databases used for post-marketing DB studies and characteristics of validation facilities should be compared for the following points, etc., to confirm that there is no significant difference that affects validation results, and it should be possible to explain that validation facilities selected have representativeness to the characteristics of medical institutions included in the medical information databases used for post-marketing DB studies.

- Differences in characteristics of medical institutions (by founder <university hospitals or clinics, etc.> and functional classification <advanced treatment

hospitals and regional medical care support hospitals>, etc.)

- Differences in patient characteristics (e.g., age, sex, and severity of the target diseases)
- Differences in each condition that make up outcome definitions (differences in distribution caused by differences in medical information coding systems, fluctuation of definition, differences in frequency of recording, and so forth)

If medical institutions included in medical information databases can be grouped based on characteristics, it may be possible to select one or more institutions from each group.

However, for example, if outcomes, for which the diagnosis or treatment is intensive to a limited number of medical institutions, are targeted, the appropriateness of outcome definitions may not be validated in an appropriate population even when the characteristics described above are taken into consideration. In such a case, it is necessary to consider a study population more specifically in advance and to include medical institutions that diagnose or treat the outcomes as validation facilities.

Even if representative medical institutions are selected based on characteristics, etc. of medical information databases, validations will be merely conducted at a limited number of institutions. Therefore, the appropriateness and limitations of applying validation results to the entire databases should be carefully considered in advance, and it should be considered to address the effects on the results, such as by performing an analysis to examine the possible impact caused by the difference between medical institutions included in the medical information databases used for post-marketing DB studies and those of validation facilities on results, in post-marketing DB studies.

5-6. Preparation of code lists and programs, etc. for data extraction

In order to appropriately extract data necessary for the validation based on the criteria for the study population and outcome definitions, it is necessary for code lists and programs, etc. after fully understanding characteristics of medical information databases (e.g., data structure, data items available for data extraction, and functional limitations in a data extraction system) to be prepared. When preparing code lists, it should be verified that all of the necessary codes are included in and obviously unnecessary codes are excluded in code lists that consists of outcome definitions by checking the appropriateness of the code masters to be referred to (e.g., version and code to be searched or extracted),

clarifying keywords etc. for extracting codes from the master, and considering characteristics of the code and actual status of coding in medical settings.

5-7. Assessment of true cases

5-7-1. How to assess true cases

When assessing true cases, it is necessary to clarify the assessment criteria and their methods so that an assessment can be made objectively as much as possible. In general, there is a method to assess based on information, such as laboratory test results or registries in which true cases are collected (e.g., hospital-based cancer registries), and a method to assess based on a medical record review. Points to consider for each method are as follows. In order to be able to assess based on the uniform criteria, regardless of the method used, it is necessary to prepare assessment forms, etc. that specifically and objectively describe the assessment criteria for cases based on opinions of clinical experts in advance, and a person assessing true cases (hereinafter referred to as "assessor") should conduct an assessment after understanding the assessment criteria.

- Laboratory test results

When laboratory test results are available, an assessment can be performed based only on laboratory test results. For example, when a test result value or its range of variation exceeds a certain level, it can be assessed as a true case. If this method is adopted, it should be prepared to present the rationale from related treatment guidelines, etc. for considering that true cases can be assessed based only on laboratory test results. It is also necessary to check whether codes and units, etc. of the target laboratory test results have been standardized in medical information databases.

- Registry

Even if it is difficult to assess based only on laboratory test results or registry, it may be possible to appropriately assess true cases by closely examining medical records. If this method is adopted, an assessor should assess whether it is a true case according to not only the presence or absence of a disease name but also records of clinical findings, such as symptoms and images, by assessing independently from a diagnosis made when the medical records are retained. Other methods may be used if the reliability of the assessment has been

confirmed in advance, but it is necessary to be able to present the rationale for ensuring the reliability.

- Review of medical records

Even if it is difficult to make a judgment based only on laboratory findings or registry, it may be possible to appropriately assess true cases by closely examining medical records. If this method is adopted, a person assessing true cases (hereinafter referred to as "assessor") should not assess whether it is a true case only by checking the presence or absence of a disease name in medical records. It is necessary to assess whether it is a true case by checking records of clinical findings, such as symptoms and images, and by assessing independently from a diagnosis made when the medical records are retained. Other methods may be used if the reliability of evaluation has been confirmed in advance, but it is necessary to be able to present the rationale for ensuring the reliability.

5-7-2. Person assessing true cases in a medical record review

When a true case is assessed by a detailed examination of medical records, it is desirable that the assessment is performed independently by two or more clinical experts per case in principle. Even if an independent assessment by two or more clinical experts is difficult, a detailed examination of medical records and assessment of true cases should be carefully planned in advance to involve clinical experts so that they can be handled objectively and uniformly. For example, there may be a method, in which a non-specialist physician performs an initial assessment and then a clinical expert performs a final assessment, or method, in which a healthcare professional other than a physician involves for, such as collection of information, necessary for an assessment and a clinical expert performs an assessment.

It is necessary to specify a procedure in advance for an assessment method of true cases when assessors give different judgements, and it is recommended to use κ coefficient, etc. to evaluate the consistency of an assessment.

5-8. Evaluation of outcome definitions

5-8-1. Indicators to be used in validation of outcome definitions

In order to evaluate the appropriateness of outcome definitions, it is desirable

to calculate PPV, sensitivity, specificity, and negative predictive value (NPV). However, it may be difficult to calculate all of these indicators from the viewpoint of feasibility when assessing true cases in a medical record review. In post-marketing DB studies, the relative risk of an exposure group compared to the control group is calculated to evaluate the strength of the relationship between exposure and outcomes, and PPV is considered to be an important indicator in evaluation of the appropriateness of outcome definitions from the viewpoint of appropriately calculating the relative risk to the control group.

In addition, in order to appropriately interpret results of post-marketing DB studies and to discuss the scope and degree, etc. of safety measures, it is necessary to understand the extent to which a population identified by outcome definitions covers the entire patients with outcomes of interest. From this perspective, the sensitivity should also be calculated secondarily in principle. The sensitivity is also considered to be a useful indicator in evaluating absolute risk and in selecting outcome definitions to be used in post-marketing DB studies from among multiple outcome definitions (see Section 5-9 for determination of outcome definitions).

Calculation of the specificity and NPV is not necessary from the viewpoint of feasibility, etc., but it is useful to consider false-positive and false-negative cases from a clinical point of view to appropriately understand characteristics of a population identified by outcome definitions.

5-8-2. Sensitivity calculation method

For the sensitivity, calculations should ideally be performed by evaluating all cases in medical information databases. However, it is often unachievable, from the viewpoint of feasibility, to evaluate all cases or a population randomly sampled from all cases with rare outcomes. In such a case, it may be effective to prepare a broad definition that is considered to identify a population assumed to include all true cases (hereinafter referred to as "all possible cases"), and identify true cases by reviewing medical records of those cases. Cases that do not meet the definition assumed as not true cases without a medical record review. Even if all possible cases are used for the validation, if it is practically difficult to conduct it because there are a considerable number of all possible cases to be reviewed for medical records, it may be an option to calculate the sensitivity based on all possible cases in a population randomly sampled after identifying all possible cases.

However, the sensitivity based on all possible cases is calculated under the assumption that all cases falling under the category of true cases are included in all possible cases; therefore, the definition of all possible cases needs to be considered carefully to meet this assumption. It should be noted that the sensitivity calculated based on all possible cases tends to be high if true cases frequently fail to be captured due to an inappropriate definition of all possible cases. Therefore, if an appropriate definition of all possible cases cannot be prepared, it may face the possibility of failing to properly evaluate the results of post-marketing DB studies, and it may be necessary to reconsider the implementation of post-marketing DB studies using the outcome definitions validated based on all possible cases.

5-8-3. Number of the target cases at the time of a medical record review

As described above, PPV and sensitivity should be examined in validation of outcome definitions in principle. But if the number of cases extracted based on the outcome definitions is large, it is often difficult to perform a medical record review for all those cases. In such a situation, it is available to randomly select the cases as targets for a medical record review, but in order to evaluate them while securing a certain level of precision, among outcome definitions to be examined in validation, it is necessary for some outcome definitions that are expected to be used in post-marketing DB studies to set the number of cases at the time of planning validation with the width of the 95% confidence interval of PPV being ± 10% or less. Ensuring a certain level of precision is important also for the sensitivity; therefore, when the sensitivity based on all possible cases is used, it is necessary to plan to be able to include 100 or more true cases in all possible cases in principle. If it is assumed that the precision of point estimates is markedly low for the sensitivity, a conservative design for the number of cases taking the precision into consideration is recommended. In order to avoid extreme differences in the number of cases subject to a medical record review, it should be planned to ensure a certain number of the subjects at each validation facility.

5-9. Determination of appropriate outcome definitions

Outcome definitions used in post-marketing DB studies are needed to be selected in consideration of the balance between PPV and sensitivity after closely examining PPV and sensitivity, etc. for all validated outcome definitions. It is appropriate to identify not only an outcome definition with the highest PPV but

also multiple outcome definitions with relatively high PPV and high sensitivity and to use these multiple outcome definitions in post-marketing DB studies. It is necessary to agree with PMDA in advance on which outcome definitions are appropriate to be used in post-marketing DB studies based on validation results.

6. Other points to consider

6-1. Publication of validation results

The validation of outcome definitions can be achieved through the understanding and cooperation of medical institutions and medical information database holders, and its implementation needs enormous resources. If there are outcome definitions whose appropriateness has been validated and if there is no major change in the medical environment, etc. compared with the time when the outcome definitions are validated, the outcome definitions can be used by persons other than those performing validation as long as they are used in medical information databases with similar characteristics, and there is no need to repeat validation for the same outcomes. From this viewpoint, it is desirable to publish validation results including their implementation method in order to promptly organize outcomes that can be used in post-marketing DB studies and to minimize resources necessary for validation. Publishing of validation results is considered important not only for promoting an appropriate implementation of post-marketing DB studies but also for ensuring transparency of results and promoting an appropriate evaluation.

6-2. Re-implementation of validation

Even for outcome definitions whose appropriateness has already been validated, the appropriateness of the outcome definitions may not be ensured when a medical information database, which is significantly different in characteristics from a medical information database used in a previous validation, is used or when the medical environment surrounding outcomes changes due to revision of clinical practice guidelines, change of standard therapy, significant change of code, and so forth after validation even if the same medical information database is used. Therefore, when outcome definitions, whose appropriateness has already been evaluated, are used, it should be checked whether a medical information database to be used has the same characteristics as a medical information database, for which outcome definitions have been validated, and at

the same time, the timing when the validation is performed and changes in the medical environment thereafter, etc. should be considered to see if the outcome definitions need to be validated again.

7. Definition of term

Terms used in this document are defined below.

DPC data	Information collected and managed by the Ministry of Health, Labour and Welfare based on Item 3, Paragraph 5 of the "Method for Calculation of the Amount of Expenses Required for Medical Treatment in Hospital Wards designated by the Minister of Health, Labour and Welfare (Ministry of Health, Labour and Welfare Notification No. 93, 2008)"
Outcome	An adverse event, etc. subject to post-marketing DB studies
Outcome definition	An algorithm for identifying the onset of outcomes in medical information databases. Typically, it is prepared by combining multiple medical information.
Sensitivity	An indicator indicating the proportion of true cases identified by outcome definitions among true cases included in medical information databases. "Sensitivity" includes sensitivity based on all possible cases unless otherwise specified.
True case	A case with the actual outcomes
Claims	A statement of medical expenses

(Appendix)

Points to consider when defining outcomes based only on laboratory test results

1. Check if several laboratory tests need to be combined to prepare outcome definitions.

Even when only laboratory test results are used to prepare outcome definitions, it is not always possible to prepare outcome definitions from one type of test results, and it may be necessary to combine several tests. For example, for neutrophil tests, it may be necessary to calculate the neutrophil count from the white blood cell count (unit: 10^3/μL) and percentage of neutrophils in white blood cells (unit: %) because the neutrophil count is not always recorded as data of test results in medical information databases. Furthermore, the percentage of neutrophils in white blood cells may be expressed as the percentage (unit: %) each of stab and segmented (further subdivided neutrophils), and it may be necessary to calculate the percentage of stab and segmented as the percentage of neutrophils in white blood cells.

2. Confirm the availability of baseline (before the start of exposure [pre-exposure]) test results.

2-1. Points to consider when defining outcomes based on test values

If outcomes are defined based on laboratory test results, laboratory test results during pre-exposure period should not be included in outcome definitions because the outcome definitions are prepared based on laboratory test results after the start of exposure (post-exposure). When defining an outcome of neutropenia according to the Common Terminology Criteria for Adverse Events (CTCAE), it is common to determine the grade of neutropenia of interest and to define the outcome by a value of neutrophil count defined by the grade.

It is necessary to consider test results during the pre-exposure period in the definition of a study population. For example, some patients may have Grade 3 or 4 neutropenia before the start of exposure, and those baseline test results should be considered in the definition (e.g., excluding cases with neutropenia before the start of exposure from a study population) of a study population.

2-2. Points to consider when defining outcomes based on relative changes from pre-exposure laboratory test results

When outcomes are defined based on relative changes in laboratory test results from pre-exposure to post-exposure, the availability of testing before the start of exposure should be confirmed because pre-exposure laboratory test results are needed. For example, the number of tests conducted before the exposure start date and the test date immediately before the exposure start date needs to be confirmed in advance. Pre-exposure laboratory test results may not be available, and therefore, the robustness of results needs to be confirmed when defining outcomes based on relative changes in laboratory test results from pre-exposure to post-exposure, for example, by considering alternative outcome definitions or performing analyses with imputation of missing values, where necessary.

2-3. Points to consider for handling of test results on the first day of exposure

In medical information databases, there may be the case where date information is available but time information is not available. Therefore, the temporal relationship between administration of the target drug and testing performed on the same day may not be clear. Whether test results on the first day of exposure should be handled as baseline test results or as post-exposure values should be considered in advance. If necessary, an analysis with changed conditions should be performed to confirm the robustness of the results.