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To: Director, Prefectural Health Department (Bureau)

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

Basic principles on Utilization of Registry for Applications

Recently, in development of drugs, medical devices, and regenerative medical products, a movement toward utilization of real world data that was obtained in the actual medical environment is gaining momentum in Japan and overseas. In japan, it is necessary to promote the utilization in clinical development by showing basic principles when an applicant utilize Registry Data, one set of real world data, for the applications.

Based on this background, “Basic Principles on Utilization of Registry for Applications” is provided in the Annex. Please inform manufacturers and sellers placed under your administration to utilize for their business operations.

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Annex

Basic Principles on Utilization of Registry for Applications

1. Background and objectives

Clinical studies are strong means to establish scientific evidence on the efficacy and safety of drugs, medical devices, and regenerative medical products and are generally required to evaluate the efficacy and safety for obtainment of marketing approval. In the review for marketing approval, the efficacy and safety are comprehensively evaluated based on the submitted data (evaluation data and reference data) with the focus on clinical data, which have been submitted to support the proposed efficacy and safety. Because clinical studies for marketing approval are focused on demonstration of the efficacy and safety, these are typically conducted as controlled studies with an appropriate control group in a carefully selected patient population in an appropriately controlled environment. In addition, randomization is used to eliminate bias that might be generated by selective allocation and accommodates critical elements in establishing a causal relationship between use of study treatment and the effect. Such stringent planning of a clinical study will ensure comparability with the control and data quality and thereby reduce the risk of making a wrong decision.

On the other hand, when the controlled studies cannot be conducted owing to the limited patient population such as orphan diseases, the following exceptional practices have been implemented[1]: A comparison between the data from an uncontrolled study and the data from an observational study on the natural history as an external control , using the survival rate as an indicator to derive the pivotal justification for the efficacy and safety; and a comparison between the data from an uncontrolled study and the data in patients who met the inclusion criteria at the site participating in the concerned study but did not receive the study treatment, using occurrence of clinically significant events. Nevertheless, there are also diseases with unmet medical needs for which drugs, medical devices, and regenerative medical products have not been developed or given the development priority owing to the extremely limited patient population, which has made conventional trial-based development difficult. The current situation surrounding such diseases requires measures that facilitate implementation of the above exceptional practices in clinical development.

Clinical studies for marketing approval, on the other hand, are not necessarily conducted in the same medical environment as actual ones. In clinical studies, patients eligible for the study treatment have to be limited to evaluate the efficacy or safety, leading to limited

information on the efficacy and safety at the approval, while the treatment, once approved, will be given to those with various characteristics.

In the current development of drugs and medical devices, therefore, an international movement toward utilization of Real World Data (hereinafter referred to as "RWD"), data obtained in the actual medical environment described below, is gaining momentum. For drugs, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (hereinafter referred to as "ICH") published the Reflection Paper for GCP Renovation[2] in January 2017 and has proposed modernization of ICH E8 (General Considerations for Clinical Trials) and subsequent revision of ICH E6 (Guideline for Good Clinical Practice) in light of diversified study designs and data sources. For medical devices, the International Medical Device Regulators Forum (IMDRF) issued three guidelines[3,4,5] for regulatory authorities regarding utilization of registry data (Principles of International System of Registries Linked to Other Data Sources and Tools [2016], Methodological Principles in the Use of International Medical Device Registry Data [2017], and Tools for Assessing the Usability of Registries in Support of Regulatory Decision-Making [2018]).

In Japan, relevant ministerial ordinances and notifications have been enforced: Ensuring reliability of data attached to the application forms for re-examination/use-results evaluation and re-evaluation using the medical information database for post-marketing surveillance of drugs, medical devices, and regenerative medical products; basic principles in utilizing medical information database on pharmacovigilance; and points to consider for ensuring the reliability of post-marketing database study of drugs, medical devices and regenerative medical products.[6,7,8,9,10,11]

For utilization of the registry data, one set of RWD, "Japan Revitalization Strategy" revised in 2015 (Cabinet decision on June 30, 2015) announced the decision to promote development in Japan by construction of novel clinical development methodologies, more specifically, to construct the disease registry system and thereby proceed with construction of the clinical innovation network (hereinafter referred to as "CIN") that develops clinical development infrastructure based on the disease registry information. Since then, construction of individual disease registries and addressing considerations to promote the CIN have been proceeded, and joint industry-academia research-and-development projects that utilize the registries have been supported.

Based on the above background, this notification has been prepared to provide Basic Principles for utilizing registry data regardless of country of the data source for the applications. The basic principles in this notification are developed for cases utilizing data only from the registry or complemented data formed by linking data from the registry to

information from the other data sources.

2. Current status and issues to be addressed

RWD data sources includes medical records , claims , data from disease registries, product registries of drugs, medical devices, or regenerative medical products, and the other healthcare data sources (such as home appliances and mobile devices).

As described in the “1. Background and objectives” section, clinical studies for marketing approval are typically focused on demonstration of the efficacy and safety and conducted as a controlled studies with an appropriate control group in a carefully selected patient population in an appropriately controlled environment and thereby provide the data, which are different from RWD obtained in an actual medical environment in terms of the quality. As described in the “1. Background and objectives” section, on the other hand, in clinical studies for marketing approval, patients eligible for the study treatment have to be limited to evaluate the efficacy or safety, leading to limited information on the efficacy and safety. If it is available to use RWD as data source explaining the efficacy and safety by referring to the below-mentioned basic principles, such a use would be beneficial, for instance, from a viewpoint of the generalization potential. Such use of RWD, when available, would promote development of treatments for diseases which have been difficult for reasons such as an extremely limited patient population.

For use of RWD for marketing approval, some issues to be addressed are raised. For instance, most of RWD are not optimized for use in efficacy and/or safety evaluation of drugs, medical devices, and regenerative medical products. In addition, data from medical records and claims are not necessarily collected or organized for research purposes. When RWD is utilized in the efficacy and/or safety evaluation to obtain marketing approvals of drugs, medical devices, and regenerative medical products, quality of the collected data should be also considered. Furthermore, when data from an observational study, especially a retrospective one, are used to explain the efficacy, a plan and analysis can be performed multiple times by changing study design elements until desirable results are obtained. For reliability assurance of the results, it is therefore important to demonstrate the reliability of the data and transparency of the study design and analysis.

The registry is a data source that has the potential to be utilized in efficacy and/or safety evaluation of drugs, medical devices and regenerative medical products, because from the registry, information of interest can be obtained in accordance with the protocol; the data quality can be assured with minimized insufficient or missing data by specifying the procedures; and follow-up information can be collected where necessary. In development of drugs, medical devices, and regenerative medical products, the registry has been

conventionally used mainly at the planning stage of clinical studies for purposes such as a market survey, proposal of clinical study protocol, inclusion of subjects in clinical studies, and investigation to determine feasibility of clinical studies. As described in the "1. Background and objectives" section, evaluation using natural history data has been also used for the applications in cases where it is difficult to conduct a controlled study owing to the limited patient population, for instance, one of rare diseases. Furthermore, registry data are expected to promote development of drugs, medical devices, and regenerative medical products when used as an external control of a clinical study or clinical data for marketing application, or utilized for application of post-marketing re-examination/use-results evaluation or re-evaluation, in view of the Basic Principles.

3. Scope

The Basic Principles shall apply to cases where registry data are utilized mainly in documents of clinical data on items included in the application or notification (applications for approval, applications for re-examination/interim evaluation inspection/use-results evaluation, application for re-evaluation, application after conditional and time-limited approval, revision of package insert [hereinafter referred to as "applications"]) for drugs, medical devices and regenerative medical products submitted in accordance with the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Product, and Cosmetics

As described in the "1. Background and objectives" section, the Basic Principles are provided mainly on the assumption that the registry data are utilized, but are partially applicable to cases where data in the placebo group in the previous trials are utilized.

Because the Basic Principles are also partially applicable to efficacy and safety evaluation for the applications, using data from medical records, the relevant applicants are strongly encouraged to refer to this notification and discuss the applicability beforehand using the consultation service offered by Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA").

4. Utilization of registry data for applications

In development of drugs, medical devices, and regenerative medical products, registry data are utilized, for instance, for the following cases (1) to (5). Of these, cases (2) to (5) correspond to ones where the applicants (or sponsors/sponsor-investigators) utilizes registry data to explain the efficacy and/or safety in documents of clinical data for the applications.

(1) Utilization of registry data in investigation of feasibility at planning of a clinical study

Disease registries are likely to be beneficial at the planning stage of clinical studies for purposes such as a market survey, proposal of clinical study protocol, inclusion of subjects in clinical studies, and investigation to determine feasibility of clinical studies, which have conventionally employed such registries, though. Especially, registry data on rare diseases are likely to be beneficial in grasping the number of patients and disease information.

Some diseases differ in severity, progression rate, affected organs, and symptoms depending on genotype or phenotype and thus present a different natural history for each subtype or have the natural history left poorly elucidated. If utilization of the registry data provides information about characteristics, symptoms, and progression rate and patterns of each subtypes, it would be useful in determining inclusion and exclusion criteria in clinical studies, disease stage to be treated, treatment period, frequency of data collection, endpoints, and target sample size.

(2) Utilization of registry data as an external control of clinical studies for efficacy and/or safety evaluation in applications.

In controlled studies, randomization is a critical procedure because it ensures comparability between groups and thereby minimizes potential bias in allocation of study treatment. For this reason, a pivotal study supporting the efficacy and safety for the applications should be basically conducted as a randomized controlled study in light of the evidence quality as long as such a study is feasible for the target diseases or investigational intervention.

There are, however, some studies that are difficult to conduct as randomized controlled studies with the control group owing to the target disease, which is rare or occurs only in children and thus has a limited patient population. In such a study, even with a limited sample size, the control group with patient characteristics matching those in subjects enrolled in the concerned study may be established by utilizing the registry data as the external control. In addition to utilization as the external control, the registry data may be used to derive a reference value with justified clinical significance for establishment of the efficacy threshold in clinical studies only including the study treatment group. For such a study, a more appropriate threshold may be established by estimating a treatment effect in the population that is formed based on individual patient data to have patient characteristics matching those in subjects enrolled in the concerned study. It should be, however, noted that the data quality may be different from that in a controlled study in

terms of study design properties such as comparability as well as data integrity and accuracy, thereby potentially affecting the efficacy and safety evaluation.

For points to consider for utilizing registry data as an external control of clinical studies for efficacy and/or safety evaluation in the applications, refer to Sections 5 and 6.

(3) Utilization of registry data as complement or substitute of clinical study for efficacy and/or safety evaluation in applications.

If the registry covers data associated with usage of the target drugs, medical devices, or regenerative medical products of interest, the concerned data may be used in efficacy and/or safety evaluation in some cases. For instance, the efficacy and/or safety of drugs or regenerative medical products already approved in Japan may be evaluated using registry data for development for indication extension and revision of package inserts in the following cases: Where the "Dosage and administration" section has been established based on conditions in the clinical studies submitted for the corresponding approval because these studies included a particular part of the patient population; and where the package insert statement limits the target population, but the drugs or products have been used in the other part of the population in clinical settings because such a use is considered to have no large impact on the efficacy or safety. In addition, the efficacy and/or safety of a medical device already approved in Japan may be also evaluated using registry data instead of clinical study data in the case where clinical studies are difficult to be conducted owing to difficulty in recruiting subjects for development for indication extension that target a pediatric or rare disease or a highly urgent disease for which immediate remedies are socially demanded owing to its significant impact on public health. Furthermore, the efficacy and/or safety may be explained using the registry data as a complement in addition to clinical study data. It should be, however, noted that utilization of the registry data may increase the generalization potential, but the data quality may be different from that in a clinical study as described in (2), thereby potentially affecting the efficacy and safety evaluation.

For points to consider for utilizing the registry for efficacy and/or safety evaluation in the applications, as a complement or alternative to the clinical studies if it covers data on drugs, medical devices, and regenerative medical products of interest, refer to Sections 5 and 7.

(4) Utilization of registry data in evaluation of drugs and medical devices with conditional approval and of regenerative medical products with conditional and time-limited approval

Registry data may be utilized in efficacy and/or safety evaluation of drugs and medical

devices with conditional approval and of regenerative medical products with conditional and time-limited approval, for instance, in the following methods. The efficacy and/or safety of drugs, medical devices, or regenerative medical products are explained by comparing its users' and non-users' data within the registry or by utilizing the registry data with the focus on results on an outcome unlikely to be affected by an investigator aware of study treatment such as a clinically objective one (e.g., overall mortality, tumor size).

For points to consider for utilizing the registry data in efficacy and/or safety evaluation of drugs and medical devices with conditional approval and of regenerative medical products with conditional and time-limited approval, refer to Sections 5 to 7.

(5) Utilization of registry data in post-marketing efficacy and/or safety evaluation

Registry data may be utilized in post-marketing efficacy and/or safety evaluation by the following methods: Efficacy and/or safety of drugs, medical devices, or regenerative medical products are explained by comparing its users' and non-users' data in clinical settings within the disease registry or based on results in the product registry. To explain the post-marketing efficacy evaluation using the registry, if applicable, refer to the Basic Principles. If an all-case surveillance assigned as a condition for approval is planned to evaluate all the investigations using the registry, the applicants have to explain that the concerned registry has enrolled all the users of the approved drugs, medical devices, or regenerative medical products.

For points to consider for utilizing registry data in post-marketing efficacy and/or safety evaluation, refer to Sections 5 to 7.

5. General points to consider

General points to consider for utilizing registry data for the applications are as follows. The followings don't indicate essential points to every situation.

In addition, when utilizing registry data for efficacy and/or safety explanation in the applications of a specific product item, the applicants should justify the concerned utilization method in the submitted data, including the purpose of the utilization, limitations of the data sources used, and a potential impact of such limitations on the results.

(1) Considerations for protection of personal information and patients' consent

For considerations for protection of personal information in and patients' consent to usage of registry data in the applications, refer to "Points to Consider for Ensuring the

Reliability in Utilization of Registry Data for Applications."

(2) Reliability of registry data utilized

Reliability of data collected should be assured according to the purpose of utilizing the registry data (refer to "Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications). If the registry data are used as the major evidence on efficacy and safety in the applications especially in the case applicable to any of 4. (2) to (5), reliability of data not only on efficacy/safety endpoints but also on factors likely to affect results from efficacy and/or safety evaluation should be ensured accordingly.

If registry data are utilized as the major evidence on the efficacy and safety of a specific product item for the applications, items required for ensuring reliability of the data may differ depending on the purpose of utilizing the registry. The applicants (or sponsors/sponsor-investigators) are therefore encouraged to discuss reliability of the concerned registry data beforehand using the consultation service offered by PMDA.

(3) Appropriateness of registry data utilized

When the registry to be used is examined according to the purpose of utilization, cautions should be taken to avoid usage of the registry data potentially leading to wrong interpretation or conclusion on development of drugs, medical devices, and regenerative medical products to be investigated, and selection of the concerned registry should be justified. If there are multiple potential registries, selection of the registry to be used must be justified by presenting reasons for selecting the concerned registry and for not selecting the other potential registries. As described in the "2. Current status and issues to be addressed" section, when registry data are used to explain the efficacy especially in a retrospective observational study, a plan and analysis can be performed multiple times by changing study design elements until desirable results are obtained, and thus appropriateness of the selection should be explained from the concerned viewpoint.

It is important to determine whether the registry data can be used in view of the purpose of utilization in both a prospective and retrospective observational study.

When foreign registry data are utilized, appropriateness of extrapolating the registry data to Japanese should be examined with reference to "Ethnic Factors in the Acceptability of Foreign Clinical Data" (PMSB Notification No. 739, ICH E5 Guideline, dated August 11, 1998).

When utilizing registry data as the major evidence on the efficacy and safety of a specific product item for the applications, the applicants (or sponsors/sponsor-investigators) are strongly encouraged to discuss the usage plan and appropriateness of positioning of the

concerned registry data in a clinical data package for the applications in view of the purpose of the utilization beforehand using the consultation service offered by PMDA.

(4) Early consultation with those who construct registry (registry holder)

There may be the following cases in utilization of registry for the applications: Utilization of the registry constructed in expectation of its usage; Consideration for utilization of the registry constructed without expectation of its usage.

If the applicants (or sponsors/sponsor-investigators) consider utilizing registry data for the applications of drugs, medical devices, or regenerative medical products, it is important to investigate registries potentially to be utilized for the applications at an early stage and consult the registry holders about identification of issues to be addressed and potential actions to be taken for such usage early.

The applicants are encouraged to discuss such matters using the consultation service offered by PMDA beforehand, taking into account the type of the registry to be used, an existing one or a newly constructed one.

6. Points to consider for utilizing registry data as an external control of clinical studies for efficacy and/or safety evaluation in applications

As described in 4. (2), the registry data may be used as an external control in cases where a randomized controlled study is difficult to be conducted. In cases where the natural history data obtained from the registry are used as an external control of a clinical study, the data used as the external control are not obtained through a randomization procedure and have bias attributable to the inclusion method and follow-up of patients, exposure of study treatment, definitions of endpoints, measuring method and measurement interval for endpoints, causing potential bias in estimation and group comparison of treatment effect. In light of this, the following points should be considered.

In addition, the followings don’t indicate essential points to every situation, and to what extent individual points should be adhered to differ depending on the situation.

Because a range of the data required differs depending on the purpose of utilization such as whether the data are to be used in evaluation for the applications, post-marketing surveillance, etc., the external control or complementary explanation, the applicants are strongly encouraged to discuss the concerned utilization using the consultation service offered by PMDA.

(1) Registry patient population

The population to be used as an external control of a clinical study should have

characteristics that potentially affect the outcome, such as disease severity, duration of the disease, and prior treatment, similar to those in the study treatment group in the clinical study to be conducted. The patient population covered by the registry, therefore, should include as many patients potentially eligible for the clinical study as possible (selected in accordance with the inclusion and exclusion criteria).

To justify the comparison using the external control, the following status should be explained: The patient population extracted from the registry in accordance with the inclusion and exclusion criteria in the clinical study have characteristics similar to those in the study treatment group in the clinical study so that the impact of such a usage on the efficacy and/or safety evaluation is minimized. A statistical analysis plan should be developed beforehand, clearly specifying the extraction conditions of patients, to explain that the data are not arbitrarily extracted for efficacy and safety evaluation, and patients eligible for the evaluation are included.

Besides a viewpoint whether the resultant populations have similar patient characteristics, if the enrollment condition differs between the registry and clinical study, the applicants should confirm that the concerned difference has minor impact, and thus the registry patient population is appropriate for evaluation of the investigational treatment.

Furthermore, the registry used should be explained to be representative of the target population of the clinical study and thus suit the purpose of utilization. In this case, distributions of the patient populations in the clinical study and registry should be explained.

For comparison with the external control, it should be noted that comparison of the efficacy and/or safety may be difficult if registry data are collected in greatly different timing from that when the clinical study is conducted, and definitions of the disease, diagnosis criteria, or the treatment system have been changed in the meantime.

For others, there may be a case where data from the placebo group in a clinical study and the natural history data are pooled for evaluation, but such pooled evaluation should be adequately justified in terms of similarity of the collected data on characteristics potentially affecting the outcome as described above and viewpoints on diagnosis criteria for a disease and treatment system as described in (5) below.

If data from registry are collected simultaneously with a clinical study, consideration should be given about whether the comparability of the patient population in the study with that from the registry can be justified because the patient population extracted from the registry in accordance with the inclusion and exclusion criteria of the study tends to include more patients who have found it difficult to participate in the study for some

reason.

(2) Endpoints

When registry data are used as an external control of a clinical study, the following cases would make it difficult to compare data on endpoints between the registry and study: Endpoints to be evaluated in the registry are not clearly defined; and the evaluation methods are not standardized. The endpoints, therefore, should be adequately justified, for instance, in terms of whether the endpoints evaluated in the study are also evaluated in the registry in accordance with the same criteria or not. If an endpoint is subjectively evaluated, measures to reduce bias such as a double-blind controlled design and evaluator training should be considered for the clinical study. If registry data are used as an external control, subjective evaluation would have bias attributable to subjects or measurers depending on perceptions about the treatment and psychological state even with measures to reduce bias such as evaluator training taken, and it would raise a concern that the bias affects comparisons between the clinical study data and registry data. Such an evaluation is unlikely to be justified. Appropriateness of the endpoints, therefore, should be carefully examined.

(3) Evaluation period

Depending on the endpoint, evaluation for an extended period is required. For prospective data collection, if any, the registry should be provided with an organization or system that ensures data collection during a period appropriate for the purpose of utilization. Registry data, collected in either prospective or retrospective manner, may be difficult to be used as an external control in the case where differences in evaluation timing for individual patients significantly compromise the comparability or where quality of the data collection is not consistent. Registry and clinical study, if both designed beforehand to provide comparable data from viewpoints of the evaluation method and timing, would have an increased possibility of data utilization. In addition, the baseline should be also specified beforehand if registry data are used as an external control.

(4) Statistical method

By adequately characterizing data to be evaluated and then exploring the statistical methods, the most appropriate method for the purpose of utilization should be selected. In addition, the statistical analysis plan should be developed beforehand to specify the statistical method to be used and criteria for the positive efficacy (or absence of the safety concern) clearly. In this statistical analysis plan, handling of missing data should be

specified as well. Furthermore, analysis procedures such as a sensitivity analysis one should be included to determine to what extent potential bias affects the results and subsequent efficacy evaluation. In addition, for the selected statistical method, its selection should be justified.

(5) Type of observational study for natural history (prospective or retrospective)

The newly constructed registry and existing registry utilized to collect data prospectively are likely to be used with the following viewpoints taken into account comprehensively.

- Data on endpoints subject to intended comparison and the other data on patients can be collected.
- For definitions of the disease, severity classification, and treatment system, the latest standard versions are consistently available.
- Standardized medical terms and measurement methods are available.
- The plan and written procedures can be prepared beforehand.
- Evaluation can be performed on a consistent schedule across patients.
- Attending physicians can be provided with standard procedures (clinical evaluation, etc.).
- Information on the same items can be collected from all patients.
- Information on time of onset, history of prior treatment, treatment course, drugs in use, basic treatment, etc. can be collected.

Especially, attention should be paid to retrospective usage of data, and the following situations can affect efficacy and/or safety evaluation. If the evaluation is significantly affected, usage of the registry may be restricted or declined.

- Data on endpoints and the other data on patients that should have been collected are not collected.
- Medical terms have been changed with time or used differently among sites participating in the registry, making it difficult to apply the terms in a standardized manner.
- Differences in evaluation timing among individual patients significantly compromise the comparability.
- Characteristics of patients in the registry are different from those of subjects in the clinical study (e.g., the natural history study targets patients only in a severe condition, while the clinical study also includes those in a mild condition).
- Records on patients are not described enough to specify onset of the disease or symptom, rationale for the diagnosis, severity, treatment course, etc.

7. Points to consider for utilizing data of drugs, medical devices and regenerative medical products from the registry for efficacy and/or safety evaluation in the applications

(1) Cases of utilizing data of drugs, medical devices and regenerative medical products from the registry for efficacy and/or safety evaluation in the application, etc.

As described in 4. (3) to (5), if registry covers data of drugs, medical devices, or regenerative medical products of interest as shown in the following cases, usage of the registry data may enable efficacy and/or safety evaluation of the products of interest. In the efficacy and/or safety evaluation, comprehensive consideration should be given to results from the previously conducted clinical studies and evidence from the registry data to be used.

① Case where the potential of the applications or revision of the package insert using the registry data is considered for drugs or regenerative medical products already approved in Japan because the scope of the approval is restricted or cautions are raised in the Precautions for Use sections (Precautions Concerning Indications, Precautions Concerning Dosage and Administration, etc.) owing to the limited clinical study results which were submitted for the existing approval and covered a particular part of the patient population, but the drugs or products have been used in the other part of the population in clinical settings.

② Case where potential of the applications in the additional part of the patient population or revision of the package insert using the registry data is considered for medical devices already approved in Japan and overseas because the clinical study results submitted for the existing approval covered only a particular part of the patient population or the disease, but the product has been used in the other part of the patient population (such as pediatric patients) in clinical settings based on the mechanism of action of the product.

③ Case where for drugs, medical devices, and regenerative medical products, clinical study results that can be used as the application data/documents are available, but the registry data are used as a complement to explain the efficacy and/or safety (e.g., the clinical studies included a particular part of the patient population).

④ Case where for drugs with conditional approval in Japan, post-marketing surveillance necessary for re-confirmation of the efficacy and safety of the concerned drugs are conducted using the registry data to submit an application for interim evaluation inspection.

⑤ Case where for medical devices with conditional approval in Japan, post-marketing surveillance necessary for re-confirmation of the efficacy and safety of the concerned medical devices are conducted using the registry data to submit an application for use-results evaluation.

⑥ Case where for regenerative medical products with conditional and time-limited approval in Japan, post-marketing surveillance necessary for re-confirmation of the efficacy and safety of the concerned regenerative products are conducted using the registry data to submit the applications.

⑦ Case where for drugs, medical devices, or regenerative medical products, post-marketing surveillance are conducted using the registry data.

⑧ Case where data on endpoints that are difficult to be specified in clinical studies (e.g., endpoints that cannot be specified owing to the limited number of patients relative to frequency of the event) or evaluated in clinical studies owing to the need of long-term evaluation are collected from the registry for the applications.

Because a range of the data required differs depending on the purpose of utilization such as whether the data are to be used in evaluation for the applications, post-marketing surveillance, etc., the substitute of a clinical study, and complementary explanation, the applicants are strongly encouraged to discuss the concerned utilization using the consultation service offered by PMDA. Points in (2) to (5) below should be considered.

(2) Patient population to be evaluated

To extract data of the patient population from the registry data, the appropriate population should be specified according to the purpose of utilizing the concerned data. Information to be extracted includes patient characteristics such as age, sex, and severity of the disease as well as factors that may significantly affect the efficacy and safety evaluation such as relevant therapies and drugs.

For instance, for utilization of the registry data as pivotal data, as described in 6. (1), a statistical analysis plan should be developed beforehand, clearly specifying the extraction conditions of patients, to explain that the data are not arbitrarily extracted for efficacy and safety evaluation, and patients eligible for the evaluation are included. In addition, for the extraction, as described in 6. (5), definitions of items entered in the registry as well as medical terms and measurement methods should be justified for use of the evaluation.

For medical devices, when the registry data are used as pivotal data alternative to a clinical study in efficacy and/or safety evaluation, it should be noted that extracted information on patient characteristics has to include not only the above-mentioned

information but also product information considered necessary for the evaluation according to properties of each medical device (information allowing identification of the product such as the product name and size and quantities used).

(3) Endpoints

Points to consider for extracting data on specific endpoints from the registry data are basically the same as those in 6. (2). The applicants are required to explain that endpoints appropriate for the purpose of utilizing the data have been selected in terms of whether definitions of individual endpoints and evaluation methods are adequately standardized in light of the purpose of utilization; whether each site has entered information on examinations and treatment in the registry in accordance with the definitions and evaluation methods; and whether the registry includes data timely appropriate for the efficacy and/or safety evaluation. In addition, for missing data, if any, the impact on the efficacy and safety evaluation should be explained.

(4) Evaluation period

Points to consider are basically the same as those in 6. (3), and follow-up evaluation in patients treated may be required depending on characteristics or intended use of the product. For instance, such an evaluation is applicable to products that are expected to become effective with post-treatment time. In such a case, the registry has to have a system that can implement follow-up and collect data continuously. The evaluation schedule and follow-up intervals are desirably specified beforehand so that each patient will be evaluated by a standardized method in light of the purpose of utilization.

(5) Statistical method

Points to consider are as described in 6. (4).

8. Conclusions

This notification represents the current principles, and its contents would be updated where necessary. In the future, accumulation of experience with utilization of registries and advances in medical information communications technologies will solve various issues currently recognized. Through adaptation to changes in situations and technologies, enhanced utilization of registries is expected.

9. Glossary

Terms in this notification are defined as follows:

Clinical study	Trial and post-marketing clinical studies conducted in accordance with the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Product, and Cosmetics
Observational study (prospective or retrospective)	Clinical research without intervention falling outside definition of clinical study. A prospective observational study is research that specifies the population of interest and collects data of outcome to be evaluated from the start of the research, while a retrospective observational study is research that specifies the population of interest using past data (data already existing at start of the research) and determines the outcome.
Real World Data (RWD)	Data on patient's health conditions and/or provided medical practices routinely collected from various data sources
Registry	A systematic system to collect standardized data to evaluate specific outcomes related to the following matters: · the specific disease · the use of drugs, medical devices and regenerative medical products, etc. · the population defined by specific conditions (e.g., age, pregnant women, specific characteristics of patients) Registry data may be prospectively obtained or retrospectively used.
Disease registry	Registry that collects data in patients with a specific disease. In addition, illness and disease are handled as the same condition (in this translated English version, "illness" is replaced by "disease"). A disease registry is one form of registry.
Product registry	Registry on a specific product of drugs, medical devices or regenerative medical products. Product registry is one form of registry.

10. References

1) "Research on measures to promote new clinical trials and clinical research based on disease registry systems (patient registry) constructed in National Centers for Advanced and Specialized Medical Care (National Centers)" General Partial Research Report of Health and Labour Sciences Research Grants FY 2015 (Health and Labour Science Special Research Project)

2) ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of ICH E6 (January 2017)

3) Principles of International System of Registries Linked to Other Data Sources and Tools (30 September, 2016)

4) Methodological Principles in the Use of International Medical Device Registry Data (16 March, 2017)

5) Tools for Assessing the Usability of Registries in Support of Regulatory Decision-Making (27 March, 2018)

6) Ministerial Ordinance for Partial Revision of the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (medical devices, regenerative medical products) (MHLW Ordinance No. 116 dated October 26, 2017)

7) Points to consider for ensuring the reliability of post-marketing database study for drugs (PSEHB/PED Notification No. 0221-1, by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated February 21, 2018)

8) Points to consider for ensuring the reliability of post-marketing database study for medical devices (PSEHB/MDED Notification No. 1219-4, by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated December 19, 2018)

9) Points to consider for ensuring the reliability of post-marketing database study for regenerative medical products (PSEHB/MDED Notification No. 0323-4, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated March 23, 2020)

10) Questions and answers (Q&A) on points to consider for ensuring the reliability of post-marketing database study for drugs (Administrative Notice, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 19, 2019)

11) Basic principles on the utilization of health information databases for Post-Marketing Surveillance of Medical Products (PSEHB/PED Notification No. 0609-8 and PSEHB/SD Notification No. 0609-4, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau and by the Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 9, 2017)