Provisional Translation (as of April 2025)*

PSB/PED Notification No. 1004-4
PSB/PSD Notification No. 1004-1
October 4, 2024

To: Director, Prefectural Health Department (Bureau)

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

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

Points to Consider When Registry Data are utilized for Partial Change Approval Applications or Revision of Electronic Package Insert for Prescription Drugs

The basic principles when registry data are used for applications for marketing approval, etc. have been described in "Basic principles on Utilization of Registry for Applications" (PSEHB/PED Notification No. 0323-1, PSEHB/MDED Notification No. 0323-1, by the Director of Pharmaceutical Evaluation Division and by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 23, 2021; hereinafter referred to as "Notification on Basic Principles"). Since the issuance of the Notification on Basic Principles, the number of cases where registry data is used as an external control or reference data for clinical studies in applications for approval, etc., has been gradually increasing.

In order to further promote the utilization of real-world data, the points to consider when registry data are utilized in procedures for partial change approval applications or revision of the electronic package insert for prescription drugs has been compiled as shown in the Annex. We ask to inform manufacturers and sellers placed under your administration to utilize this for their business operations.

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* 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

Points to Consider When Registry Data are utilized for Partial Change Approval Applications or Revision of Electronic Package Insert for Prescription Drugs

1 Background and Purpose

Recently, discussions on the use of Real World Data (hereinafter referred to as "RWD") in procedures including those for approval applications for prescription drugs have been further promoted in Japan. With respect to registry data, one type of RWD, the principles on utilization of the data for approval application, etc. have been described in "Basic Principles on Utilization of Registry for Applications" (PSEHB/PED Notification No. 0323-1, PSEHB/MDED Notification No. 0323-1, by the Director of Pharmaceutical Evaluation Division and by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 23, 2021; hereinafter referred to as "Notification on Basic Principles").

In order to demonstrate the efficacy and safety of a prescription drug for marketing approval, it is generally necessary to conduct clinical trials that serve as evaluation data. However, in cases where it is difficult to conduct clinical trials for reasons such as an extremely small number of patients, e.g. in case of rare diseases, it is expected that the development of the prescription drug will be promoted by using registry data as an external control or as a substitute for clinical trials.

The Notification on Basic Principles also states the utilization of registry data to complement or substitute for clinical trials in evaluating efficacy and/or safety in application for approval, etc.. In the relevant statement, it is described that "efficacy and/or safety 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 are limited to some patient groups or target patients are limits in the package insert statement limits the target population, but the drugs or products have been used in other part of the population in clinical settings because such a use is considered to have no large impact on the efficacy or the safety."

This notification provides points to consider for use of registry data in partial change approval applications for additional indications and new dosage and administration of approved prescription drugs (hereinafter referred to as partial change) or revision (deletion, addition, and modification) of sections of “Precautions concerning indications,” “Precautions concerning Dosage and Administration,” and “Clinical studies” in the electronic package insert (hereinafter referred to as electronic PI) among utilization of

registry data listed in the Notification on Basic Principles.

2 When registry data are utilized for partial change for prescription drugs

For partial changes for the additional indication or new dosage and administration or changes to the approved indication or dosage and administration of prescription drugs, registry data may be used as evaluation data to substitute for clinical study results if there is an existing registry that can be used in the application and that appropriately reflects the characteristics of the target population, and if the efficacy and/or safety of the indication, etc. can be evaluated from the registry and reliable data can be obtained from the registry. In particular, with regard to addition of indications, dosage and administration, etc. for rare diseases and pediatric for which clinical studies are difficult to conduct, it is meaningful to examine a potential to implement a partial change using registry data.

For using registry data as evaluation data, it is assumed that the collected data will be analyzed based on an appropriate survey plan, etc. and that its reliability will be ensured. Therefore, it is strongly recommended to use the consultation service offered by the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") to discuss plans concerning the target population, endpoints, analysis methods, etc., and the reliability of registry data in advance from the stage of planning the survey plan, etc.

In the case of a partial change using registry data, not only evaluation data using registry data but also clinical trial results at the time of approval for the approved indications, data on the actual use in the clinical practice concerning the indication for which a partial change is to be made, and data used for regulatory approval in foreign countries (countries that have approval system that are recognized to be at the same level as Japan or equivalent systems [e.g. the U.S., and Europe; the same shall apply hereinafter]), and information including Japanese and overseas clinical guidelines may serve as important supplementary data.

When considering making a partial change by attaching existing registry data as evaluation data instead of clinical trial results, it is strongly recommended to consider available information other than registry data and use the consultation service offered by PMDA to discuss the appropriateness of the application data package before making the application.

3 When registry data are utilized for revision of the electronic PI of prescription drugs

In "Amendment of the Instructions for Electronic Package Inserts Regarding Results of Studies Using Medical Information Database" (PSEHB Notification No. 0217-1 by the Director-General of Pharmaceutical Safety and Environmental Health Bureau, Ministry

of Health, Labour and Welfare, dated February 17, 2023) and "Points to Consider for Describing the Results of Studies Using Medical Information Database in Electronic Package Inserts" (PSEHB/SD Notification No. 0217-1 by the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated February 17, 2023), it is stated that the results of studies using medical information database shall be described in "17.2 Post-marketing surveillance, etc." section of the electronic PI for some patient groups corresponding to the section "9. Precautions concerning patients with specific backgrounds" in electronic PIs of prescription drugs for which sufficient safety data have not been obtained.

The sections of "5. Precautions concerning indications,"7. Precautions concerning dosage and administration," "9. Precautions concerning patients with specific backgrounds," "17.1 Clinical studies for efficacy and safety," and "17.2 Post-marketing surveillance, etc." of the electronic PI of prescription drugs usually contain precautions for appropriate target patients for the administration and precautions concerning administration methods or clinical study results that serve as the rationale for the precautions, based on the results of clinical studies and post-marketing surveillance, etc. It may be possible to revise the contents of the precautions in the electronic PI for the purpose of reflecting the actual use in clinical practice, when results requiring attention to the approved indication or dosage and administration are obtained; when major evidence that serve as a substitute for clinical trial results are obtained in patient groups for whom efficacy data have not been obtained for the approved indications or dosage and administration; or when important results that supplement "Clinical studies for efficacy and safety" are obtained in patients for whom sufficient efficacy data have not been obtained, as a result of the use of existing registry data.

If revision of the electronic PI of a prescription drug using existing registry data is considered, it is recommended to use the consultation service offered by PMDA to discuss the plans concerning the target population, endpoints, analysis methods, etc., necessity of revision of the electronic PI, reliability of registry data, etc. from the stage of planning of the survey plan, etc. In addition, when analysis results using registry data are obtained and actually a consultation is made with PMDA, consultation associated with revision of package inserts of drugs (Consultation on prior confirmation of revision of package inserts for drugs and Consultation on revision of package inserts for drugs) and Consultation on compliance inspections of supporting data for revision of package inserts for drugs that are offered by PMDA should be utilized.

4 Other points to consider

(1) It should be fully noted that this notification does not recommend off-label use for the purpose of a partial change. Clinical studies should be conducted when off-label

use is to be newly performed for the purpose of a partial change and information is to be collected.

(2) When making a partial change or revising the electronic PI using registry data, personal information should be handled based on the Act on the Protection of Personal Information (Act No. 57 of 2003), etc.

(3) When data using registry data are submitted as evaluation data for a partial change, these data should be submitted as (g) (data concerning test results of clinical studies, etc.) specified in Article 40, Paragraph 1, Item 1 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHW Ordinance No. 1, 1961).

(4) When data using registry data are submitted as evaluation data for a partial change or used as the evidence for revision of the electronic PI, the reliability of such data needs to be ensured. Specifically, the records/documents should be appropriately stored, and the records/documents (including records/documents related to the operation and management of registry holders and records/documents for information sources as necessary) should be accessible at the time of compliance inspection or consultation. Regarding the reliability of registry data, applicants or persons seeking consultations must guarantee that the reliability of registry data is ensured at their own responsibility by referring to related notifications, etc.[1) 2)] in advance. When using registry data that have not been used for pharmaceutical affairs, consultation should be made with PMDA about matters necessary for securing the reliability, particularly from the stage of planning the survey plan, etc.

(5) This notification provides points to consider when registry data are used in development for expansion of indications and revision of electronic PI, etc. based on the principles shown in the Notification of Basic Principles. However, contents of this notification may apply to the use of other RWD including databases that collect data such as medical records based on consideration of characteristics of the data, etc.

(6) This notification provides points to consider at present, and it should be noted that these points may change depending on the accumulation of cases of utilization, new knowledge to be obtained in the future and advances in science and technology, domestic and overseas regulatory status, etc.

5 References

1) "Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications" (PSEHB/PED Notification No. 0323-2, PSEHB/MDED Notification No. 0323-2, by the Director of Pharmaceutical Evaluation Division and by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March

23, 2021)

2) Questions and Answers (Q&A) on Points to consider for Ensuring the Reliability in Utilization of Data from Registry or Medical Information Database in Applications for Marketing Approval and Re-examination for Drugs (Administrative Notice, by Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated September 14, 2022)