

Provisional Translation (as of May 2021)*

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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

**Points to Consider for Ensuring the Reliability in Utilization of
Registry Data for Applications**

Registry data is one of real-world data obtained under clinical practice. In development of drugs, medical devices and regenerative medical products, when an applicant utilizes registry data, it is important to ensure the reliability of registry data.

Based on this background, “Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications” is provided in the Annex. Please inform manufacturers and sellers placed under your administration to utilize this 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.

Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications

1. Purpose of the points to consider

This notification indicates the points to consider for ensuring the reliability in utilization of data from the registries (hereinafter referred to as "registry data ") when the applicant (including sponsor and sponsor-investigator; the same shall apply hereinafter) intends to utilize registry data as a clinical data (evaluation data) in the data/documents to be submitted for the following applications of drugs, medical devices, and regenerative medical products (hereinafter referred to as "Application data/documents"),

- Application for marketing approval
- Application for re-examination
- Application for interim evaluation
- Application for use-results evaluation
- Application for re-evaluation
- Application after conditional and time-limited approval

The scope of this notification includes not only the registries to be newly constructed but also the registries that have been constructed with accumulated data. With regard to the significance of utilization of registry data and the basic principles for such utilization, refer to "Basic Principles on utilization of registry for applications" (hereinafter referred to as "Basic Principles on Utilization").

2. Concepts of ensuring the reliability

A registry is constructed for the purpose of conducting studies related to the followings:

- the specific disease
- the use of drugs, medical devices, and regenerative medical products, etc.
- the populations defined by specific conditions (e.g., age, pregnant women, characteristics of specific patients)

Since registry data is collected according to the original purpose of registries, the concepts and methods adopted to ensure reliability of registry data vary. Also, in the case of secondary utilization of registry data as Application data/documents., etc., the level of reliability required for the registry data may vary depending on the purpose

of utilization (refer to "Basic Principles on Utilization"). Therefore, an applicant is not required to ensure all the matters provided in this notification in a unified manner. But an applicant is required to consider necessary matters on case by case basis according to the purpose of utilization. Consequently, in the case of utilization of registry data as Application data/documents, etc., an applicant is encouraged to consult Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") regarding necessary matters, etc. to ensure the reliability of registry data in Application data/documents., etc.

3. Concepts of ensuring the reliability in utilization of registry data as Application data/documents for marketing approval

The following matters are specified for an applicant to utilize registry data as Application data/documents for marketing approval.

- Compliance matters for applicants utilizing registry data
- Points to consider for registry data utilized for application data/documents

This notification should also be referred to when an applicant intends to utilize registry data for Post-marketing clinical studies in the applications for reexamination/use-results evaluation, etc.

(1) Compliance matters for applicants utilizing registry data

1) Confirmation of data quality management implemented by registry holders

In considering the utilization of registry data, an applicant should confirm the quality of the registry data to determine whether the intended use can be adequately fulfilled. When making the determination, an applicant should refer to "(2) Points to consider for the registry utilized as application data/documents for marketing approval" described later.

For prospectively collected registry data, an applicant shall confirm that registry holders manage the quality of the registry by, for example, reviewing quality management records of registry data provided by the registry holders. In addition, for retrospectively collected registry data or registry data which have not been managed enough, the applicant is encouraged to consult PMDA because the approach to confirm the reliability of such registry data needs to be carefully examined.

2) Contracts with registry holders

Before datasets or analysis results, etc. are received from a registry holder, an applicant shall appropriately conclude a contract with the registry holder. At that time, an applicant shall be able to explain how reliability of the registry data is ensured by, for example, requesting the registry holder to

provide documents such as operating procedures and operation records.

3) Statistical analysis

When an applicant executes statistical analysis utilizing datasets received from a registry holder, an applicant shall predetermine procedures and plans, and execute statistical analysis as specified in Statistical Analysis Plan, etc. in accordance with those procedures and plans. When a registry holder executes statistical analysis, a registry holder shall also predetermine procedures and plans, and executes statistical analysis in accordance with those procedures and plans.

4) Preparation of application data/documents

An applicant shall predetermine procedures, and prepare application data/documents in accordance with the procedures with being kept in mind the following matters: Accuracy and Comprehensiveness

5) Storage of records

When an applicant prepares application data/documents utilizing registry data, an applicant shall predetermine procedures, and store records/documents of the studies in accordance with the procedures. In addition, an applicant shall confirm the storage status, etc. of the records/documents stored by the registry holders.

(2) Points to consider for the registry utilized as application data/documents for marketing approval

1) Governance by registry holders

In order for reliable registry data to be maintained by registry holders, the following matters are important:

- appropriate handling of individual data
- continuous maintenance and management of the registry
- securing the transparency of operation of the registry

[1] Establishment of operation and management system

In order to appropriately handle individual registry data and continuously operate and manage the registry, registry holders shall specify the operations and procedures required and establish appropriate operation and management system.

[2] Policy on securing transparency

Considering the effect on decision making based on collection and analysis of registry data and results of the analysis, registry holders shall specify and publish the policies on the following matters necessary to secure the transparency of the operation and management of the registry.

- Conflict of interest
- Operation and management system of registry holders, etc.
- Funding for the registry
- Purpose of the registry
- Disclosure of data, etc.

[3] Policy on access to registry data

Since the registry contains confidential information related to the patient's health condition and/or treatment, etc., registry holders shall specify rules on the method for accessing the registry data and the access limitations for users (including the case where the regulatory authorities access the data).

In addition, registry holders shall specify the following matters as needed.

- Methods of application for access to registry data
- Criteria to determine the appropriateness of the contents of application for access

2) Computerized system

Collection routes of registry data are highly diversified, and in recent years, registry holders may collect registry data efficiently utilizing a computerized system in connection with systems located in various information sources.

When registry holders collect registry data utilizing a computerized system, an applicant shall confirm the status and contents of the following matters implemented by registry holders.

- Quality management of the computerized system
- Preservation of security of confidential information related to the patient's health condition and/or treatment, etc.
- Backup and recovery of data

[1] Quality management of the computerized system

Methods of quality management of the computerized system may vary depending on the purpose of each registry, etc.

Registry holders shall implement the following matters appropriately and efficiently according to the configuration of the computerized system.

- Implementation of computerized system validation based on risk assessment at the time of introduction or update of the computerized system
- Confirmation of the operating status of the computerized system to

be utilized

- Establishment of the authenticity, visual readability, and storage property of electromagnetic records by specifications and operation methods of the computerized system

Refer also to the following notification, which includes points to consider when an applicant handles records/documents for application data/documents as electromagnetic records: "Use of Electromagnetic Records and Electronic Signatures for Application for Marketing Approval or Licensing of drugs, etc." (PFSB Notification No. 0401022, by the Director-General of Pharmaceutical and Food Safety Bureau, MHLW, dated April 1, 2005.

[2] Security of computerized system

Registry holders shall specify the overall security of the computerized system to be utilized and implement it in accordance with the procedures.

In particular, the following matters shall be specified.

- Scope of access limitations for users of the computerized systems according to the contents of registry data
- Education and training for users of the computerized system regarding the overall computerized system, security requirements, and registry-specific handling
- Network security

[3] Backup and recovery of registry data

Registry holders shall specify the methods of backup and recovery of registry data and implement them in accordance with the procedures.

3) Quality Management of registry data

Since registry holders implement quality management of registry data according to the original purpose of the registry, an applicant shall determine whether quality management is appropriate for the applicant's purposes of utilization by reviewing the contents of quality management implemented by registry holders.

Points to consider when an applicant reviews the contents of quality management of registry data are illustrated as follows. As described above, since the level of reliability required for registry data vary depending on the status and purpose of utilization of the registry, an applicant is encouraged to consult PMDA about methods for quality management together with registry holders at the time when the applicant decide to utilize registry data

as application data/documents.

[1] Data collection methods

There are many potential routes to collect registry data. Regardless of the data collection routes, registry holders shall specify the methods to appropriately collect predetermined survey items and implement data collection in accordance with the procedure.

Examples of matters to be confirmed

- Procedures for writing/entering data
- Clarification of persons who write/enter the data
- Education and training for persons who write/enter the data

[2] Handling of collected registry data

Registry holders shall predetermine procedures and handle the collected data in accordance with the procedures. In addition, registry holders shall fix and store the data collected from information source in accordance with the predetermined procedures by registry holders.

Examples of matters to be confirmed

- Methods for anonymizing data when users access the registry data or registry holders provide the registry data to users because registry data contains confidential information
- Procedures for data cleaning (including procedures for confirming the information source about any inquiries raised as a result of data cleaning)
- Procedures for recording a history of data correction
- Procedures for coding data
- Procedures for fixing data

[3] Monitoring

If registry holders implement monitoring, registry holders shall predetermine procedures for monitoring and implement in accordance with the procedures. It is desirable that applicants confirm the records at the information source as needed. In addition, registry holders shall have obtained consent regarding monitoring, either directly or through the information source, from patients who provide data to the registry.

With regard to the procedure for monitoring, refer to "Basic Principles on Risk-Based Monitoring in Clinical Trials" (PSEHB/PED Notification No. 0705-7 by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW dated July 5, 2019).

[4] Quality management for data migration from hospital information system, etc. to a computerized system

If the registry has been established to migrate data to a computerized system from the hospital information system, etc., registry holders shall confirm the following matters.

- The computerized system is operating as designed.
- The data from information source are migrated to the computerized system as designed.
- Data migration is not affected by update of hospital information system, etc. and changes in entry items, etc. in the computerized system.

With regard to quality management and quality assurance by registry holders, refer to "Basic Principles on Quality Management in Clinical Trials" (PSEHB/PED Notification No. 0705-5 by Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW dated July 5, 2019).

4) Quality Assurance for Registry

Registry holders shall confirm that they have assured the following matters according to the original purpose of the registry and the quality of registry data.

- the governance by the registry holder is maintained
- the quality of registry data is managed

It is desirable that an applicant confirm the procedures and the records, etc. of quality assurance implemented in accordance with the procedures, as needed.

5) Data Extraction and Datasets Preparation

When an applicant utilize registry data as application data/documents, the statistical analysis of registry data can be classified into the following two cases.

- Registry holders perform the operations from extracting data to execution of the statistical analysis.
- An applicant receives datasets from registry holders and execute the statistical analysis.

In either case, registry holders shall predetermine procedures for appropriately extracting registry data to be utilized from the fixed data and conduct extraction in accordance with the procedures.

In case that an applicant receives datasets from registry holders and executes

statistical analysis, it is important that an applicant shall present Statistical Analysis Plan, etc. to registry holders and agree on the scope (range and condition, etc.) of datasets prepared by registry holders before data extraction.

4. Consideration for protection of personal information

Protection of personal information should be considered regardless of the methods of data quality management. When registry data are utilized as application data/document, the registry holders will provide the registry data to an applicant. Therefore applicants and registry holders should give consideration to protection of personal information of patients.

An applicant shall confirm that registry holders have specified the requirements and procedures related to consent of a patient who provides data to the registry, in accordance with the following regulations.

- Act on the Protection of Personal Information
- Other applicable regulatory requirements

When consent of a patient is obtained, an applicant shall confirm that the informed consent form includes necessary information.

If there is a possibility that a third party (monitors, auditors, regulatory authorities, etc.) will access source documents, etc. stored at the information source, an applicant shall confirm that the informed consent form includes the description of this access as needed.

5. Concept of ensuring the reliability when registry data are utilized as application data/documents for reexamination or use-results evaluation, etc.

When registry data are utilized for post-marketing database study specified in the following ministerial ordinances:

- Ministerial Ordinance on Good Post-Marketing Study for Drugs (MHLW Ordinance No. 171 of 2004)
- Ministerial Ordinance on Good Post-Marketing Study for Medical Devices (MHLW Ordinance No. 38 of 2005)
- Ministerial Ordinance on Post-Marketing Study for Regenerative Medical Products (MHLW Ordinance No. 90 of 2014),

The following notifications shall be referred to:

- 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, MHLW, dated February 21, 2018)

- Points to consider for ensuring the reliability of post-marketing database study for medical devices (Notification No. 1219-4 by the Director of the Medical Device Evaluation Division, MHLW, dated December 19, 2018)
- 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 the Medical Device Evaluation Division, MHLW, dated March 23, 2020)
- 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, MHLW, dated June 19, 2019)

6. Others

This notification is based on the knowledge obtained at present, and will be revised appropriately in consideration of matters such as the followings:

- Accumulated cases of utilization of registry data as Application data/document
- Advance in medical information communication technology
- Trends of international discussions

For individual cases not included in this notification, applicants and registry holders are encouraged to consult PMDA about the reliability of registry data.

7. Definitions of terms

The definitions of terms in this notification are as follows.

Terms	Definitions
Registry	A systematic system to collect standardized data to evaluate specific outcomes related to the following matters <ul style="list-style-type: none"> • the specific disease • the use of drugs, regenerative medical products, or medical devices, etc. • the populations defined by specific conditions (e.g., age, pregnant women, specific characteristics of patients) Registry data may be prospectively obtained or retrospectively used.
Registry holders	Persons/organizations who mainly manage and operate registry and hold registry data
Applicant	A marketing authorization holder, etc. who intends to submit application for marketing approval, etc. of drugs, medical devices, or regenerative medical products by utilizing registry data.
Information source	Medical institutions or laboratories, etc. which provide

	data to registry holders
Source documents	Records necessary for the reconstruction and evaluation of the study such as hospital records and laboratory notes
Computerized system	System in general to electronically collect and manage registry data
Data cleaning	Data management of a registry by deleting or correcting registry data, etc.
Coding	Data management of a registry by replacing registry data with predetermined numerical values/code, etc. to process registry data efficiently
Dataset	Data extracted from the registry based on predetermined scope (range and condition, etc.) to prepare Application data/document., etc.

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