Provisional Translation (as of April 2023)*

Administrative Notice
March 31, 2023

To: Prefectural Health Department (Bureau)

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

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 Regenerative Medical Products

Basic concepts for using real-world data such as those in registries or medical information databases (hereinafter referred to as "MID") for applications for marketing approval, re-examination, etc. have been shown in the following notifications: "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 Directors of the Pharmaceutical Evaluation Division and the Medical Device Evaluation Division, MHLW, dated March 23, 2021) and "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).

With the accumulation of cases of consultations on reliability of the registry or MID in the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA"), general points to consider in confirming reliability of the registry or MID that is planned to be used when an applicant, etc. uses the data from the registry or MID for applications for marketing approval of regenerative medical products, re-examination, etc. were organized as questions and answers (Q&A) in an Annex.

Please inform manufacturers and sellers placed under your administration to utilize this Q&A for their business operations.

Q&A will be reviewed as needed based on the accumulation of cases of consultations at the PMDA, technical progress of registries or databases, and changes in overseas regulatory status, etc.

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* This English version of the Japanese Administrative Notice 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)

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 Regenerative Medical Products

* The following abbreviations are used in this Q&A.

"Notification for Database Reliability" "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 Devices Evaluation Division, Pharmaceutical Safety and Ministry of Health, Labour and Welfare dated March 23, 2020) "Notification for Registry Reliability" "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 Directors of the Pharmaceutical Evaluation Division and Medical Device Evaluation Division, MHLW, dated March 23, 2021) "Notifications for RWD Reliability" A general term for Notification for Database Reliability and Notification for Registry Reliability "Pharmaceuticals and Medical Devices Act" "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Act No. 145 dated August 10,1960) "Enforcement Regulation of the Act" "Ministerial Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Ministry of Health and Welfare Ordinance No. 1 of 1961) "GPSP Ordinance" "Ministerial Ordinance on Good Post-marketing Study Practice for Regenerative Medical Products" (Ministry of Health, Labour and Welfare Ordinance No.90 of 2014)

"PMDA"
Pharmaceuticals and Medical Devices Agency

"Re-examination, etc."
Approval review after conditional and time-limited authorization, re-examination and re-evaluation

"Medical information"
Electronic medical information such as data from the hospital information system (electronic medical record, diagnosis procedure combination [DPC], etc.), data of claims for medical fees and dispensing fees (including receipt data of health insurance associations), and disease registry data

"Post-marketing database studies"
A study conducted by utilizing the medical information database (hereinafter referred to as "MID") provided by a MID holder as specified in Article 2, Paragraph 1, Item (2) of the GPSP Ordinance to retrieve or confirm occurrence status of defects or adverse events of regenerative medical products by disease category and information on quality, efficacy and safety

"Medical Information Database"
An aggregate of information related to medical records and other records of medical practices, claims for medical fees, and disease registration which is collected for a certain period of time and systematically constructed

"DB holder"
A MID holder as specified in "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 Devices Evaluation Division, Pharmaceutical Safety and Ministry of Health, Labour and Welfare dated March 23, 2020)

"Applicant, etc."
An applicant or a marketing authorization holder of regenerative medical products, including a designated holder of marketing authorization for foreign-manufactured

regenerative medical products, who intends to submit an application for marketing approval, re-examination, re-evaluation and approval review after conditional and time-limited authorization, utilizing the data from registry or MID

"Registry"
A systematic system to collect standardized data to evaluate specific outcomes related to the following matters:

- 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 holder"
Persons/organizations who mainly manage and operate registry and hold registry data

"Information source"
Medical institutions, laboratories, etc. which provide data to registry holders or DB 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 data

"Next Generation Medical Infrastructure Act"
"Act on Anonymized Medical Data That Are Meant to Contribute to Research and Development in the Medical Field" (Act No. 28 dated May 12, 2017)

"Personal Information Protection Law"
"Act on the Protection of Personal Information" (Act No. 57 dated May 30, 2003)

"Data cleaning"
Data management of MID by deleting or correcting medical information

"Coding"
Data management of MID by replacing medical information with numerical values/code, etc. to process medical information efficiently on a computer

(1) Matters common to studies using registries and post-marketing database studies

Q1:
Is it acceptable for an applicant, etc. to limit the contents to be confirmed with a registry holder or DB holder regarding registry and MID to the part related to the study?

A1:
Yes. The part related to the study to be utilized as application data/documents for approval and re-examination are subject to the confirmation.

Q2:
When conducting a study with registry or MID, does an applicant, etc. need to prepare documents to ensure the reliability to registry or MID for each study protocol?

A2:
In principle, it needs to be prepared. However, when an applicant, etc. simultaneously conducts multiple studies utilizing the same registry or MID, or when the applicant, etc. has previously conducted a study utilizing the same registry or MID, all or part of preparation of documents to ensure the reliability of the registry holder or the DB holder can be omitted for the newly conducted study, if the applicant, etc. can prove that the following conditions are satisfied:

- The contents of confirmation of operating procedures, etc. related to the reliability of registry or MID at the initial study are recorded.
- In the registry holder, DB holder or the information source, the system configuration of registry or MID and operating procedures, etc. have not been changed.
- Any matters of concern that should be additionally confirmed have not occurred since the initial study.

In such a case, it is necessary for the applicant, etc. to be able to explain the validity of the omission.

Q3:
Is it acceptable to confirm the reliability of the registry or MID to be used by an applicant, etc. just before the start of the study using the data?

A3:
If it is found that the reliability of the data from the registry or MID to be used cannot be guaranteed, it is necessary to review the plan of the proposed study even at the stage when the planning of the study has been completed. Therefore, an applicant, etc. should confirm it at the earliest possible stage of the planning of the study.

If any question arises in the confirmation, consult with PMDA when necessary.

Q4:
What should be noted when revealing that some of the necessary operations/procedures have not been specified or the necessary written procedures have not been prepared for some period after confirming the reliability of the registry or MID to be used by an applicant, etc.?

A4:
If the operations/procedures that have not been specified are needed to support the use of the registry or MID, it is necessary for an applicant, etc. to discuss whether the operations/procedures can be specified with the registry holder or the DB holder. If possible, the applicant, etc. should request the registry holder or the DB holder to specify the operations/procedures as early as possible.

During the period when some of the necessary operations/procedures are not specified, the applicant should confirm that the registry holder or the DB holder ensures that there is no problem in the operation/management system and there is no impact on the quality of the collected data, and the registry holder or the DB holder retains its records. The availability of data from the registry or the MID during the relevant period and actions to be taken in the case where it cannot be confirmed should be consulted with PMDA as needed.

Q5:
In some cases, the names of operations and procedures relating to the operation and management of the registry or MID may not be the same as those provided in the Notifications for RWD Reliability. If the names do not match, is it acceptable for an

applicant, etc. to confirm that the necessary operations and procedures shown in the Notifications for RWD Reliability are specified and the operations are conducted appropriately in accordance with the procedures, and explain it by linking the names with the actual names?

A5:

Yes. The names of operations and procedures relating to the operation and management of the registry or MID need not be the same as those provided in the Notifications for RWD Reliability. However, an applicant, etc. should link the name shown in the Notifications for RWD Reliability with the actual name so that it can be explained to the inspector in regulatory authorities.

Q6:

When the procedure and frequency of data quality management by the registry holder or the DB vendor holder are confirmed by an applicant, etc. and it becomes clear that quality management has not been performed sufficiently for the data items to be used, can the data be used as application data for approval or re-examinations of regenerative medical products or application data for re-examinations of regenerative medical products by additional actions such as quality management taken by the registry holder or the DB holder?

A6:

In principle, it is inappropriate to take additional actions such as quality management after the analysis results are obtained for data that are considered important for review. However, before the analysis results are obtained, the data may be used as application data for approval or re-examinations of regenerative medical products by taking additional measures such as quality management for studies for which the data are to be used. The appropriateness of taking additional actions such as quality management should be discussed with the registry holder or the DB holder, and the PMDA should be consulted where necessary.

Q7:

Is it acceptable to confirm the reliability of the registry or MID which an applicant, etc. plans to use only by hearings without reviewing the written procedures and supporting data for operations possessed by the registry holder or the DB holder?

A7:

It is important for an applicant, etc. to confirm the reliability by reviewing the written procedures for each operation and supporting data, etc. held by the registry holder or the DB holder, and it is not appropriate to confirm only by hearings. It is important for the applicant, etc. to review the supporting data presented by the registry holder or the DB holder to confirm that the registry holder or the DB holder specifies the operating procedures necessary for operation and management and work while keeping records based on the procedures. If there are no rules for review to supporting data, it is necessary to consult with the registry holder or the DB holder to specify the rules.

Such a confirmation shall be made based on an appropriate confidentiality agreement. Therefore, no supporting data that cannot be viewed by the applicant, etc. are assumed, except for data that may cause critical difficulty in the operations of the registry holder or the DB holder. However, if there are any supporting data not presented by the registry holder or the DB holder, the applicant, etc. should consult with the PMDA as needed after grasping the reason for not being presented by the registry holder or the DB holder, the outline of the contents described, and the possibility of confirming the contents from other supporting data. However, if the applicant, etc. has a concern, etc. about the supporting data not presented by the registry holder or the DB holder, or if the inspector in regulatory authorities examines them in the compliance inspection, those supporting data should be accessible, and therefore it is necessary to discuss measures to make them available with the registry holder or the DB holder.

Q8:

In the Notifications for RWD Reliability, an applicant, etc. is required to appropriately conclude a contract with the registry holder or DB holder. Are there any items to be included in the contract other than basic items necessary for the use of data from registries or MIDs, such as:

- Date of conclusion of the contract,
- Contract period,
- Persons who concluded the contract,
- Matters related to the confidentiality agreement, and
- Data to be provided?

A8:

In addition to basic items necessary for the use of data from registries or MIDs, the contract should also include the following items:

- Documents (including data) related to operations for quality management, quality assurance, etc. in registries or MIDs should be stored for the period specified in Article 43, Item 3 or Article 61 of the Enforcement Regulation of the Act
- When making an application for marketing approval, re-examination, etc. by using the data from the registry or the MID provided to an applicant, etc., cooperation should be given in the compliance inspection conducted based on the Pharmaceuticals and Medical Devices Act, such as review to the data by the regulatory authorities
- In order to confirm whether the reliability of the data from the registry or the MID used by an applicant, etc. for an application for marketing approval, re-examination, etc., is ensured, the registry holder or the DB holder should cooperate in providing review to the retained data
- If there is a possibility that the reliability of the data in the registry or the MID provided to an applicant, etc. may be affected due to a system failure or other problems., the registry holder or the DB holder should promptly contact the applicant, etc. and report the results of measures taken

Even for matters other than items above, if there are any matters necessary for the use of data from registries or MIDs, an applicant, etc. should appropriately conclude a contract. If it is handled by describing it in other documents such as the study protocol, it is acceptable not to include it in the contract text.

Q9: When confirming the reliability of the registry or MID to be used, it was found out that the data obtained from the information source were corrected or deleted by the registry holder or DB holder. What points should an applicant, etc. confirm from the viewpoint of ensuring quality of data?

A9:

An applicant, etc. should confirm:

- Whether the conditions and procedures for data correction or deletion are specified in advance by the registry holder or the DB holder,
- Whether the operations are performed while keeping records according to the procedures,
- What data are actually corrected or deleted at what frequency from the implementation records, and keep the records.

The applicant, etc. should confirm whether the conditions for correction or deletion of

data specified by the registry holder or the DB holder have been established with rationale, and where necessary, the validity has been confirmed with the information source, and also investigate the impact on the study based on the contents, frequency, etc. of the corrected or deleted data. If there is any question, consult with PMDA as needed.

Q10:
In regard to data collected by registry holders and DB holders, restrictions such as lack of data and biases in data distribution may occur to a certain degree in the collected data due to the characteristics of the registry or MID, even when data quality management is continuously performed. How should an applicant, etc. handle such restrictions?

A10:
When using data from registries or MIDs, an applicant, etc. should confirm in advance whether there are any restrictions for use, and then consider and record any influence on the study. It is also necessary to explain this to the inspectors in regulatory authorities who review at the time of an application for marketing approval, re-examination, etc. For example, it may be possible to clarify restrictions in the protocol, report, etc. of the study to be conducted. If there is any concern, it is desirable to consult with the PMDA before submitting an application for marketing approval or re-examination, etc. as needed.

Q11:
How will compliance inspections be conducted in applications for marketing approval, re-examination, etc. using data from registries or MIDs?

A11:
In the compliance inspection, the results of how an applicant, etc. confirmed data held by the registry holder or the DB holder will be examined in order to confirm whether the reliability of application data for approval or re-examinations of regenerative medical products are ensured. If the regulatory authorities judge it necessary to investigate the data held by the registry holder or the DB holder as a result of examination mentioned above, such data will also be also investigated. In this case, not all materials stored by the registry holder or the DB holder will be investigated comprehensively, but materials related to the concerns should be investigated according to its risks. Since it is not

acceptable not to disclose supporting data necessary to ensure the reliability of application data for approval or re-examinations of regenerative medical products among the data stored by the registry holder or the DB holder in the compliance inspection, it should be specified in the contract that the applicant, etc. will cooperate in the compliance inspection as described in Q&A8 of this notification when concluding a contract with the registry holder or the DB holder. In addition, the applicant, etc. should request the registry holder or the DB holder, etc. to allow the regulatory authorities to review the supporting data, etc. so that the compliance inspection can be implemented smoothly. Before an application for marketing approval, re-examination, etc., the applicant, etc. should discuss the method, scope, etc. of access to supporting data by regulatory authorities with the registry holder or the DB holder, and if read-only access authority is necessary for the inspectors in charge, the applicant, etc. should also request the registry holder or the DB holder to take actions accordingly. Since the compliance inspection by the regulatory authorities is conducted based on the law, limiting information access for reasons specified in the Personal Information Protection Law or limiting access by third party shall not apply.

Q12:

For a data backup and recovery when the registry holder or the DB holder collects data using a computerized system, is it acceptable for the applicant, etc. to ensure it by checking its implementation procedures and confirming that a backup is actually performed at a frequency specified in advance, from the viewpoint of risk avoidance, and that data can be recovered from a backup if system trouble, etc. occurs?

A12:

Yes. It is acceptable to ensure a backup and recovery from the viewpoint of risk avoidance. Note that when data cannot be recovered from a backup if system trouble, etc. occurs, the data may not be available for applications for marketing approval, re-examination, etc.

(2) Matters related to studies using registries

Q13:

Data not collected in the registry or not specified to be collected in the study protocol of registry, etc. were required for the purposes of applications for marketing approval, re-examination, etc. When we consulted with the registry holder, it replied that it was

possible to additionally obtain data. In this case, is it necessary for the applicant, etc. to confirm what kind of procedures have been performed?

A13:

An applicant, etc. should confirm and keep records of the following matters:

- Obtaining additional data from the registry by the registry holder is within the scope of data to be collected from the registry specified in the document (study protocol or appropriate document),
- Necessary procedures are taken for the change (including revision of the study protocol, etc., revision of the written informed consent form, and reobtaining informed consent based on the revised informed consent form as needed.) through the registry holder based on the rules at the information source, and
- How the additional data are obtained.

Q14:

The Notification for Registry Reliability requires clarification of procedures and personnel, and education and training for writing/entering data. What are the points to consider for an applicant, etc. when confirming the reliability of a registry that is planned to be used if there is any case report form completed or data entered on Electronic Data Capture (EDC) by healthcare professionals other than physicians?

A14:

It depends on the intended use of registry data, but in principle, it is necessary that the data in the case report form or EDC be confirmed by a physician similarly to clinical trials (post-marketing clinical studies) or use-results surveys. When EDC is used, it is necessary to provide education and training to the healthcare professionals concerned, to appropriately control the account, and to identify the person who entered data with audit trails. In addition, it is possible to utilize a system to transfer data from the system owned by the information source to EDC, but in that case, it is necessary to confirm that appropriate system validation is performed at the time of system introduction or update and it is guaranteed that data can be transferred accurately and completely.

Even if it has not been confirmed by a physician, entry in the registry at the information source may be appropriately controlled and quality management by the registry holder may be sufficiently performed, as in the case of collecting data, etc. to be used for health insurance. Whether such data can be utilized will be determined for each intended use, and therefore consult with PMDA as needed.

Q15:

It is explained in the Notification for Registry Reliability that "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." When confirming the reliability of the registry to be used, does the applicant, etc. need to confirm whether consent has been obtained from information sources for the possibility that the relevant data are provided to regulatory authorities and used for an application for marketing approval?

A15:

When using data obtained from the registry for an application for marketing approval, it is necessary to obtain the principal's consent at the information source in writing or by an appropriate method regarding the possibility that the data may be provided to the regulatory authorities and used for an application for marketing approval, unless otherwise specified by laws and regulations. An applicant, etc. should confirm the status of obtaining informed consent at the information source through the registry holder and keep a record.

Q16:

The Notification for Registry Reliability requires "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." If the written informed consent form does not include a statement that the regulatory authorities may have access to the source documents, etc. stored in the information source, will it be impossible to use the data from the registry in the application data for approval or re-examination of regenerative medical products because the regulatory authorities cannot conduct the inspection?

A16:

Compliance inspections by regulatory authorities are conducted based on laws and regulations, and therefore even if there is no such statement, there is no problem in terms of the Personal Information Protection Law, and it is possible to conduct inspections when necessary. The absence of such a statement does not preclude the use

of data from the registry in application data for approval or re-examinations of regenerative medical products, but from the viewpoint of providing a detailed explanation to data providers, it is recommended to add the possibility of review to source documents, etc. by regulatory authorities to the written informed consent form as soon as possible.

Note that if the regulatory authority cannot review the data for a reason such as inability to obtain the cooperation of the information source despite the regulatory authority judging it necessary to review the data from the information source, the data about which questions arise may not be used for an application for marketing approval, re-examination, etc.

(3) Matters related to post-marketing database studies

Q17: Does Notification for Database Reliability indicate matters to consider when an applicant, etc. conducts a post-marketing database study specified in Article 2, Paragraph 1, Item 2 of the GPSP ordinance?

A17:

Yes. Therefore, the use-results survey specified in Article 2, Paragraph 1 of the GPSP ordinance is not subject to the Notification for Database Reliability (For example, the case where the use-results survey is conducted utilizing a Disease registry database constructed to conduct the use-results survey based on the GPSP ordinance prior to its revision). From the viewpoint of ensuring the reliability of application data/documents, however, an applicant, etc. may utilize Notification for Database Reliability as a reference, as needed, even if an applicant, etc. utilizes a database established under a contract directly concluded with a medical institution for the use-results survey.

Q18: According to Notification for Database Reliability 3. (2) a, it is specified that an applicant, etc. shall confirm the methods for the DB holder to confirm that medical information has been correctly captured when the DB holder collects the medical information from the information sources. What are the points to consider when MID is constructed by a DB holder who collects the medical information by migration, etc. from the information source for secondary utilization of the data?

A18:

From the viewpoint of consistency of the contents and the number of cases between medical information entered in the hospital information system, etc. by the information source (original data) and medical information captured into MID, an applicant, etc. shall ensure that appropriate verification has been performed by a DB holder. If the verification has been performed appropriately by the information source, that verification may be deemed as a substitute for the verification to be performed by a DB holder. In such a case, however, an applicant, etc. shall confirm that the DB holder has reviewed the method and results of the verification performed by the information source and keep the records of the confirmation.

Verification is not necessarily required to confirm an exact match between the original data and the medical information captured into MID. However, the extent to be confirmed that the original data are correctly captured into MID and the cause and extent of impact in the case that correct capture cannot be confirmed should be evaluated by the information source or DB holder, and an applicant, etc. needs to confirm its appropriateness. Regarding the verification that the original data have been correctly captured into MID, the applicant, etc. shall confirm procedures and records of the verification while paying attention to the following matters:

- The process is clarified in procedures, etc., and the verification results obtained from the process have been recorded and stored appropriately.
- Consistency has been verified based on the real data of a certain period held by each information source (original data entered/obtained for the purpose of actual medical practice, etc. at the information source), not the sample data created virtually.
- Since the method of operating the hospital information system, etc. and systems utilized in each department (e.g., medical accounting system connected within the hospital information system, operation system of the laboratory test department), etc. in the information source may be changed, the verification has been performed not only at the initial stage of construction of MID but also periodically with continuity (Refer to Notification for Database Reliability 3. (2) c and this Notification Q&A24).

Q19:

Q&A18 of this notification explains points to consider in the case where the MID is collected and constructed with migration, etc. of medical information from the information source by a vendor of the information source or a DB holder for the purpose of secondary utilization of data. Is it correct to understand that this does not

apply to the case where data are collected by using EDC in the registry?

A19:

Yes. If data are collected using EDC in the registry, the contents of Q&A18 of this notification are not applicable because the method of data quality management is different.

Q20:

Q&A18 of this notification explains that it is necessary to confirm that the DB holder is verifying the medical information (original data) and the database data for the MID which collects the data related to medical records and other records of medical practices. What is the scope of verification necessary to be confirmed from the viewpoint of consistency of contents and number of cases for the MID which collects the claims for medical fees?

A20:

It is necessary to confirm that the MID that collects claims for medical fees is validated to the following extent:

- It is not necessary to confirm the process from medical information (original data) to the database of the health insurance association and examination and payment organization in medical care, etc. because the accuracy is publicly guaranteed, if the data of the database accumulated in the health insurance association and examination and payment organization in medical care, etc. are used. The procedures or operation records such as the process where the data of the relevant database are saved in the database of the DB holder and the process until the data to be used are extracted from the database of the DB holder should be confirmed
- If the medical institution provides the DB holder with the files to be submitted to the health insurance association, examination and payment organization in medical care, etc. or the processed files, and the DB holder has constructed the database based on such files, it is not necessary to confirm the output process of such files from the medical information (original data) because the accuracy is publicly guaranteed. The procedures or work records such as the process of preparing and providing the relevant files or processed files, the process of saving the data of such files or processed files in the database of the DB holder, and the process until the data to be used are extracted from the database of the DB holder should be confirmed
- If the medical institution manually prepares and provides the DB holder with

medical data files or their processed files from hospital information system, etc. using the function of the hospital information system that ensures the reliability, and the database is constructed by the DB holder based on the files, the procedures and operation records including the process of manually preparing and providing the files, the process of saving the data of the files or processed files in the database of the DB holder, and the process until the data to be used are output from the database of the DB holder should be confirmed

This data collection may be performed by more than one route. If it is difficult to make a judgment, consult with the PMDA as needed.

Q21:
Is it correct that the medical information (original data) shown in Q&A20 of this notification refers to the data entered in the hospital information system, etc.?

A21:
Yes.

Q22:
In Q&A18 of this notification, it is specified that an applicant, etc. should confirm that the DB holder has performed appropriate verification from the viewpoint of consistency of contents and number of cases. How should the applicant, etc. confirm it concretely?

A22:
An applicant, etc. should confirm the results of extraction and comparison by the DB holder of raw data for a fixed period extracted from the medical information (original data) and the DB holder's MID by using operation records, etc. (procedures and operation records, and if applicable, records of training for persons conducting comparison). For such a comparison, if it is not possible to directly compare the data extracted from each, it is acceptable to clarify the process in the data flow and confirm the results of comparison for each process based on the operation records. In addition, it should be confirmed that the medical information (original data) to be used for such a comparison is data extracted by a method that ensures the reliability, which is different from the function of data extraction developed to output from the system that possesses the medical information (original data) to the MID.

If there is no update of the system, etc., periodic confirmation may be substituted by

confirmation of records such as the save status of data by DB holder.

Q23:
Q&A18 of this notification specifies “the points to consider when MID is constructed by a DB holder who collects the medical information by migration, etc. from the information source for secondary utilization of the data.” Is it necessary for an applicant, etc. to confirm records of computerized system validation conducted by DB holder at the time of construction and update of the hospital information system at the information source as well as at the time of introduction and update of the function of output, etc. of claims data and Diagnosis Procedure Combination (DPC)?

A23:
Q&A18 of this notification does not require that records of computerized system validation be confirmed at medical institutions when the hospital information system is constructed as well as when the function of output, etc. of claims data and Diagnosis Procedure Combination (DPC) is introduced and updated.

Q24:
In Notification for Database Reliability 3. (2) a, it is specified that “an applicant shall confirm these matters (related to quality management of medical information collected from the information sources) not only at the selection of MID but also at other timing as needed.” What timing should an applicant, etc. confirm these matters in addition to the time of selecting MID of MID?

A24:
The following timings are assumed:

- When the method of operating hospital information system, etc. and/or systems, etc. utilized in each department at an information source are changed
- When the rules and/or procedures for construction of MID are changed
- When questions arise about the appropriateness of the procedures of DB holders

Q25:
According to Notification for Database Reliability 3. (2) a, it is specified that an applicant, etc. shall confirm the standards and procedures for data cleaning and/or coding, and then shall confirm that the relevant operations have been implemented appropriately. Does an applicant, etc. have any particular points to consider?

A25:

In data cleaning and/or coding, if practical operations in the information source are not appropriately reflected based on predetermined implementation standards and procedures, an unintended discrepancy between the original data and modified data may occur, leading to erroneous analysis results.

The standards and procedures for data cleaning and coding and the contents of implementation should be appropriately recorded by a DB holder, and an applicant, etc. should be able to confirm the records. In particular, an applicant, etc. should confirm the following matters:

- For data cleaning, the standards and procedures for data modification implemented by a DB holder and the records of the modification
- For coding, the standards and procedures of a DB holder to confirm the actual operations implemented at each information source and the records proving that the DB holder actually confirmed with the information source.

For example, for coding in order to appropriately assign the necessary standard code to the data of the laboratory test, it is considered necessary to grasp not only the information on the analyte, but also the information on materials of the laboratory sample and measurement methods. If a standard code is assigned based only on information such as a test name or code unique to each medical institution, there is a possibility that a standard code may not be appropriately assigned, for example, the same standard code may be assigned to different codes for which the source tissue of the materials or measurement methods are completely different.

Q26:

In Notification for Database Reliability 3. (2) c, it is specified that "an applicant, etc. shall confirm that a DB holder continuously manages the quality of MID by receiving the quality management records periodically related to medical information provided by the DB holder." How frequently do you assume the records should be received?

A26:

An applicant, etc. shall set the frequency necessary to continuously ensure the reliability of MID to be utilized for the post-marketing database study based on the following matters:

- The frequency of collection of medical information by a DB holder from information sources

- The frequency of changes of the method of operating hospital information system, etc. and/or changes in systems utilized in each department
- The frequency of changes in rules, etc. for construction of MID

Q27:
In Notification for Database Reliability 3. (2) c, it is specified that "an applicant, etc. shall confirm that a DB holder continuously manages the quality of MID." What are points to consider when an applicant, etc. confirms the continuous quality management performed by DB holders?

A27:
The points for which continuous quality management is required are assumed to be the following matters, etc.:

- Errors in migration of data at the time of capture of medical information
- Errors in data extraction and in analysis systems

To confirm that a DB holder can appropriately respond to the occurrence of these errors, etc., an applicant, etc. shall pay attention to the following matters specifically.

- In the rules, etc. for quality management, procedures for promptly detecting and handling errors, etc. have been established.
- A system to promptly resolve errors, etc. has been established.
- Regarding the errors, etc., the date of occurrence (or the date of detection), the details and action taken have been recorded appropriately, and the records can be confirmed

by an applicant, etc.

Q28:
What are points to consider when an applicant, etc. concludes a contract with a DB holder to conduct a post-marketing database study?

A28:
The operations for which applicants, etc. conclude a contract with DB holders are assumed to be the following, etc.:

- Preparation of datasets for analysis
- Preparation of analysis results
- Preparation of documents indicating that they have been prepared appropriately

An applicant, etc. needs to conclude a contract for operations related to preparation of

datasets for analysis with a DB holder based on Article 6, a provision to be applied Mutatis Mutandis pursuant to Article 6-2 of the GPSP ordinance.

If an applicant, etc. requests a DB holder to perform operations related to the preparation of analysis results without obtaining the datasets for analysis from the DB holder, in addition to the contract for the operations related to the preparation of datasets for analysis mentioned above, the applicant, etc. needs to conclude a contract for the operations related to the preparation of analysis results based on either Article 6, a provision to be applied Mutatis Mutandis pursuant to Article 6-2 of the GPSP ordinance, or Article 10, Paragraph 2. However, the applicant, etc. may decide which provision will be selected as the basis of the contract.

In contrast, if an applicant, etc. obtains the datasets for analysis from a DB holder and then requests a DB holder to perform operations related to the preparation of analysis results utilizing the preceding datasets for analysis, the applicant, etc. needs to conclude a contract for the operations related to the preparation of analysis results based on Article 10, Paragraph 2 of the GPSP ordinance. Obtaining the datasets in this context includes not only receiving the datasets as actual documents, etc. but also the cases where the applicant, etc. can access the electromagnetic records of the datasets.

Regardless of whether the contract is based on Article 6, a provision to be applied Mutatis Mutandis pursuant to Article 6-2 of the GPSP ordinance, or Article 10, Paragraph 2, an applicant, etc. needs to confirm that preparation of datasets for analysis and operations of analysis are appropriately executed by a DB holder based on the protocol for the post- marketing database study or SAP by reviewing the documents indicating that datasets for analysis and analysis results are appropriately prepared. It should be fully noted that these documents are subject to confirmation at the compliance inspection and an applicant, etc. shall obtain these documents from a DB holder. (If these documents cannot be obtained, it is judged that the reliability of the results of the post-marketing database study as the application data/documents for re-examination has not been assured.)

Q29: Are there any points for an applicant, etc. to consider from the viewpoint of protection of personal information when conducting a post-marketing database study?

A29:

In the post-marketing database study, the applicant, etc. utilizes medical information collected by a DB holder instead of collecting information directly from healthcare

professionals at medical institutions, etc. according to the provision of Article 68, Paragraph 2-5 of Pharmaceutical and Medical Device Act. (excluding the case where medical information obtained in cooperation with medical institutions, academic organizations, etc. is used pursuant to the provision of the same article.)

When conducting a post-marketing database study, DB holders are required to handle personal information appropriately. On that basis, an applicant, etc. shall consider that specific procedures of a DB holder for collecting and providing medical information (e.g., acquisition of informed consent, anonymization, handling based on the Next Generation Medical Infrastructure Act) have been performed in compliance with Personal Information Protection Law and other relevant laws, regulations and guidelines.

Q30: The Notification for Database Reliability requires an applicant, etc. to check the business plan for handling of the MID. The business plan includes matters other than those related to operation and management of the MID. If the positioning of the MID to be used and the business continuity, etc. can be determined, is it acceptable to check only the relevant descriptions, not all of the business plan? In addition, is it acceptable to confirm with documents other than the business plan if similar contents are included?

A30:

Yes. It is acceptable to confirm the positioning of the MID to be used and the business continuity, etc. in a part of the business plan or other documents.

Q31: Is it acceptable to omit the preparation of the SAP when the contents to be described in the SAP are described in the post-marketing database study protocol?

A31:

You may omit the preparation. If the contents to be described in the SAP are not described in the post-marketing database study protocol, for example, in the case when operations of analysis are outsourced to a contract research organization, an applicant, etc. shall prepare the SAP separately in an appropriate manner.

(4) Others

Q32:

Can an applicant, etc. conduct a study utilizing registry or MID provided by a foreign registry holder or DB holder containing medical information collected from information sources in Japan?

A32:

Yes. When registry or MID provided by registry holder or DB holder is utilized, an applicant, etc. needs to comply with Notification for RWD Reliability and this Notification regardless of whether the database is provided by Japanese or foreign registry holder or DB holder.

Q33:

An applicant, etc. should confirm the reliability of the MID to be used when using the data from the MID for an application for marketing approval. The Notification for Database Reliability and Q&A (3) of this notification summarize points to consider regarding ensuring reliability in post-marketing database studies for regenerative medical products. When utilizing them for an application for marketing approval of regenerative medical products, is it acceptable to confirm reliability of the MID to be used by referring to these notifications?

A33:

Yes. An applicant, etc. should confirm the reliability of the MID to be used with reference to the Notification for Database Reliability and Q&A of this notification when using the data from the MID for an application for marketing approval. If there is any question, consult with PMDA as needed.