Provisional Translation (as of December 2021)*

Administrative Notice
June 19, 2019

To: Prefectural Health Department (Bureau)

Pharmaceutical 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 of Post-marketing Database Study for Drugs

Questions and answers (Q&A) concerning "Points to Consider for Ensuring the Reliability of Post-marketing Database Study for Drugs" (PSEHB/PED Notification No. 0221-1 dated February 21, 2018) are provided in the Annex. Please inform manufacturers and sellers placed under your administration to utilize this Q&A for their business operations.

* 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 of Post-marketing Database Study for Drugs

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

"Notification for Reliability" "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, Ministry of Health, Labour and Welfare dated February 21, 2018)"
"Pharmaceutical and Medical Device Act" "The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics" (Act No. 145 dated August 10,1960)
"GPSP ordinance" "Ministerial Ordinance on Good Post-marketing Study Practice for Drugs (Ministry of Health, Labour and Welfare Ordinance No.171 of 2004) "
"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 so that the information can be retrieved utilizing a computer as specified in Article 2, paragraph 2 of the GPSP ordinance
"DB holder" A medical information database (hereinafter referred to as "MID") holder who provides MID for business use as specified in Article 2, Paragraph 3 of the GPSP ordinance.
"MAH, etc." Marketing authorization holders of drugs or designated holders of marketing authorization for foreign-manufactured drugs, etc.

"Applicant"
An MAH, etc. who intends to submit an application for re-examination, etc. of drugs utilizing the results of post-marketing database studies

"ER/ES Guideline"
"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)

"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)

<General matters>

Q1:
From what viewpoint does an applicant need to confirm MID that a DB holder has constructed and operated?

A1:
An applicant shall confirm that a DB holder has constructed and operated MID in an appropriate method and ensured the authenticity, visual readability, and storage properties of medical information. To ensure the reliability of application/data documents, the ER/ES Guideline, which is a guideline for ensuring the authenticity, visual readability, and storage properties of electromagnetic records, shall also be referred to, as needed.

<Scope of application>

Q2:
Can an applicant conduct a post-marketing database study utilizing MID provided by a foreign DB holder containing medical information collected from information sources in Japan?

A2:
Yes. When MID provided by DB holders is utilized, an applicant needs to comply with Notification for Reliability regardless of whether the database is provided by Japanese or foreign DB holders.

Q3: Does Notification for Reliability indicate matters to consider when an applicant conducts a post-marketing database study specified in Article 2, Paragraph 1, Item 2 of the GPSP ordinance?

A3:
Yes. Therefore, the use-results survey specified in Article 2, Paragraph 1 of the GPSP ordinance is not subject to the Notification for 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 may utilize Notification for Reliability as a reference, as needed, even if an applicant utilizes a database established under a contract directly concluded with a medical institution for the use-results survey.

Q4: Is it acceptable for an applicant to limit the contents to be confirmed with a DB holder regarding MID based on 3 (1) and (2) of Notification for Reliability to the part related to the post-marketing database study?

A4:
As described in your question, the part related to the post-marketing database study to be utilized as application data/documents for re-examination is subject to the confirmation.

<Preparation of Statistical Analysis Plan (SAP)>

Q5: 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?

A5:
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 shall prepare the SAP separately in an appropriate manner.

<Selection of MID and contract with DB holders>

Q6: What are points to consider when an applicant concludes a contract with a DB holder to conduct a post-marketing database study?

A6:
The operations for which applicants 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 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 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 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 may decide which provision will be selected as the basis of the contract.
In contrast, if an applicant 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 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 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 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 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.)

Q7: When conducting a post-marketing database study, does an applicant need to prepare documents to ensure the reliability based on Notification for Reliability for each post-marketing database study protocol?

A7:

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

- The contents of confirmation of operating procedures, etc. related to the reliability of MID at the initial study are recorded.
- In the DB holder or the information source, the system configuration of 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 to be able to explain the validity of the omission.

<Quality management of medical information collected from information source>

Q8: According to Notification for Reliability 3. (2) a, it is described that an applicant 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?

A8:

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 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 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 needs to confirm its appropriateness.

Regarding the verification that the original data have been correctly captured into MID, the applicant 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 Reliability 3. (2) c and Q9).

Q9:

In Notification for Reliability 3. (2) a, it is described 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 timings as needed. What timing should an applicant confirm these matters “except for the time of

selection” of MID?

A9:

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

Q10: In Notification for Reliability 3. (2) c, it is described that “an applicant 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?

A10:

An applicant 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

Q11: In Notification for Reliability 3. (2) c, it is described that “an applicant shall confirm that a DB holder continuously manages the quality of MID.” What are points to consider when an applicant confirms the continuous quality management performed by DB holders?

A11:

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 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.

<Standards and procedures for data cleaning and coding>

Q12: According to Notification for Reliability 3. (2) a, it is described that an applicant 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 have any particular points to consider?

A12:

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 should be able to confirm the records. In particular, an applicant 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.

<Other points to consider>

Q13: Are there any points for an applicant to consider from the viewpoint of protection of personal information when conducting a post-marketing database study?

A13:

In the post-marketing database study, the MAH, 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 of Pharmaceutical and Medical Device Act. When conducting a post-marketing database study, DB holders are required to handle personal information appropriately. On that basis, an applicant 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.