Administrative Notice
December 26, 2023

To: Prefectural Health Departments (Bureaus)

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

Revision of Questions and Answers (Q&A) for Periodic Reporting of Cases of Adverse Reactions, etc. in Clinical Trials

Handling of periodic reports of cases of adverse reactions, etc. in clinical trials based on Article 273 of the Regulation 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) has been shown in "Points to Consider for Periodic Reporting of Cases of Adverse Reactions, etc. in Clinical Trials" (PSEHB/PED Notification No. 0831-14 of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020; hereinafter referred to as the "Clinical Trial Periodic Report Director Notification") and "Revision of Questions and Answers (Q&A) for Periodic Reporting of Cases of Adverse Reactions, etc. in Clinical Trials" (PSEHB/PED Administrative Notice of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 30, 2023; hereinafter referred to as the "Old Administrative Notice").

We have recently changed the questions and answers (Q&A) for periodic reports of cases of adverse reactions, etc. in clinical trials as shown in the attachment. Please inform related businesses and medical institutions, etc. under your jurisdiction of the change.

With the issuance of this administrative notice, the Old Administrative Notice will be abolished.

Please note that a copy of this administrative notice will be sent to the related organizations in the attached list, Pharmaceuticals and Medical Devices Agency, and each regional bureau of health and welfare.

(Attachment)

Questions and Answers (Q&A) for Periodic Reports of Cases of Adverse Reactions, etc. in Clinical Trials

* The additions and changes made as of December 26, 2023 are underlined.

<Base date for annual report>

Q1

If wishing to set a base date for an annual report on a date other than the date of the first notification, the Development International Birth Date, or International Birth Date, what should be done specifically?

A1

Before changing the base date for reporting for annual reports, submit the “Request for change of a base date for reporting” to the Review Planning Division, Office of Review Management, Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”). In the “Request for change of a base date for reporting” (free format), enter the “test substance identification code,” “original base date,” “new base date,” “reason for changing a base date,” and “next scheduled survey unit period."

For annual reports for which the base date has been changed to a date other than the date of the first notification, the Development International Birth Date, or the International Birth Date, describe this in the remarks column of Attached Form 1.

For study drugs other than test drugs, requests for changes of base dates are not required.

<Resumption of annual reports>

Q2

How should the base date be considered when resuming annual reports in association with the resumption of clinical trials of the active ingredient concerned for development for additional indications, etc.?

A2

In principle, one of the dates on which integral multiples of one year have passed since the original base date for annual reports before resumption, which comes immediately before the date of submission of the notification for resumption of development, shall be used as the base date to make annual reports. When setting a date other than the base date before resumption as the base date at the time of resumption, refer to Q1.

<Resumption of annual reports>

Q3

How should the number of reports in Attached Form 1 be counted when resuming annual reports in association with the resumption of clinical trials of the active ingredient concerned for development for additional indications, etc.?

A3

Count the number consecutively following the most recent report.

<Attached Form 1>

Q4

How should the column for “Information on study drugs other than the test drug” be filled out when there are multiple study drugs other than the test drug concerned?

A4

List the generic names and the use (comparator, concomitant drug, rescue drug, etc.) written in the notification, and provide the information (the test substance identification code of the main test drug and the number of notifications) indicating the clinical trials in which the study drugs concerned have been used.

<Attached Form 1>

Q5

In the column for “Comments and safety measures based on accumulation and evaluation of serious adverse reactions and other safety information (nonclinical study data, overseas clinical study data, post-marketing data, etc.),” can the information be described for each study drug?

A5

Yes.

<Attached Form 2>

Q6

In 2. of the attachment for the Clinical Trial Periodic Report Director Notification, it states that “For study drugs other than the test drug, it is acceptable to prepare the list for the clinical trials ongoing or completed during the survey period concerned.” If the cumulative number of events for the study drugs other than the test drug cannot be calculated, can the number of events for cases of adverse reactions, etc. associated with study drugs other than the test drug by type during the “survey unit period” be considered the same as the “cumulative” number of events?

A6

If the cumulative number cannot be calculated, such a description is acceptable. In this case, enter in the remarks column of Attached Form 1 that the number of events during the “survey unit period” and the “cumulative” number of events are the same value.

<Attached Form 2>

Q7

For the test drug, from which time point should the cumulative number of events for the list of occurrence status of domestic cases of serious adverse reactions, etc. in Attached Form 2 be calculated?

A7

In principle, enter the cumulative number of events for cases of serious adverse reactions, etc. reported from clinical trials conducted in Japan from the time of the first clinical trial notification for the test drug concerned in Japan. If information on cases of serious adverse reactions, etc. is obtained from clinical trials other than those for which notifications were made by the sponsor/sponsor-investigator concerned, the cumulative number reflecting the information shall be entered.

When making one annual report for multiple test drugs with the same active ingredient, the cumulative number of events from the cases related to the test drug for which the clinical trial notification was made earliest shall be presented.

Data may be tabulated separately by test drug, dosage form, administration route, etc. In such cases, explain this in the remarks column of Attached Form 2.

<Attached Form 2>

Q8

If the comparator is an active drug and a study drug, how should cases of adverse reactions, etc. be tabulated under blinded conditions?

A8

It is acceptable to tabulate the data as those of the test drug under blinded conditions.

<Attached Form 2>

Q9

For the cumulative number of events related to study drugs other than the test drug to be entered in the List of Occurrence Status of Domestic Cases of Serious Adverse Reactions, etc. in Attached Form 2, is it acceptable to enter only the information obtained in the clinical trial concerned?

A9

In order to accurately understand the tendency of occurrence of adverse reactions, etc., it is desirable to enter the cumulative number of events for cases of serious adverse reactions, etc. reported in clinical trials conducted in Japan wherever possible for study drugs other than the test drug, as is the case with test drugs.

<Attached Form 2>

Q10

For study drugs other than the test drug described when switching a notification made according to previous rules (hereinafter referred to as “old form”) based on the “Handling of Notifications, etc. of Clinical Trial Plans Related To Drugs by Persons Who Intend to Sponsor Clinical Trials” (PSEHB/PED Notification No. 0831-10 of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020) or “Handling of Notifications, etc. of Clinical Trial Plans for Drugs by Persons Who Intend to Be Sponsor-investigators” (PSEHB/PED Notification No. 0831-11 of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau,

Ministry of Health, Labour and Welfare, dated August 31, 2020) to a clinical trial notification according to these notifications (hereinafter referred to as “new form”), is it necessary to include the adverse reactions, etc. obtained before the submission of the notification in the new form in the number of events to be entered in the List of Occurrence Status of Domestic Cases of Serious Adverse Reactions, etc. in Attached Form 2?

A10

It is not necessary.

<Notification of annual report to medical institutions>

Q11

Even if a list of occurrence status of domestic cases of serious adverse reactions, etc. (Attached Form 2) has been prepared with unblinded information for reporting to the regulatory authorities, is it acceptable to prepare Attached Form 2 based on the blinded information and use it to notify medical institutions if the clinical trial in Japan needs to be kept blinded?

A11

Yes.

<MedDRA version>

Q12

It is required to use the same version of Medical Dictionary for Regulatory Activities/Japanese version (hereinafter referred to as “MedDRA/J”) for the list of occurrence status of domestic cases of serious adverse reactions, etc. (Attached Form 2) throughout the survey unit period concerned. Is it possible to use another version during other survey unit periods?

A12

It is possible, but the version of MedDRA/J used should be clearly presented.

<Annual report when both clinical trials and post-marketing clinical studies are conducted>

Q13

How should the information obtained from post-marketing clinical studies be included in the Development Safety Update Report (DSUR)?

A13

When preparing a DSUR, the information obtained from post-marketing clinical studies shall be included in the DSUR (see “Development Safety Update Report” [PFSB/ELD Notification No. 1228-1 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated December 28, 2012]). In this case, data from the post-marketing clinical studies and important safety findings shall be described in the respective corresponding sections.

If there is any important safety information, describe it also in Attached Form 1 of the annual report. In Attached Form 2 of the annual report, it is sufficient to describe the serious adverse reactions, etc. reported from clinical trials. Therefore, information obtained from post-marketing clinical studies does not necessarily have to be included.

<Notification to medical institutions of post-marketing clinical studies>

Q14

If a post-marketing clinical study is ongoing during the period of a clinical trial for a partial change in indications, etc. for a drug approved in Japan, which form should be used in notifying medical institutions conducting the post-marketing clinical study of an annual report?

A14

Prepare Attached Form 2 describing serious adverse reactions, etc. from the post-marketing clinical study concerned and notify medical institutions of it.

<Notification of annual report to medical institutions>

Q15

Is it necessary to notify investigators and heads of medical institutions of Attached Forms 1 and 2 even if there are no cases of serious adverse reactions, etc. to be tabulated in clinical trials in Japan during the survey unit period?

A15

During the clinical trial period, development safety information shall be investigated based on the information from all the sources (nonclinical studies, literature, post-marketing studies, etc.) that can be obtained during the development period to prepare a DSUR. At least while subjects are participating in clinical trials, it is necessary to notify medical institutions of Attached Form 1 and 2 of the annual report, which is a summary of DSUR, whether or not cases of serious adverse reactions, etc. occurred.

<When annual report is not required>

Q16

What studies will not require annual reporting?

A16

The following studies are applicable. If the annual report is not required, it is not necessary to submit any of Attached Form 1 or 2, or DSUR.

[1] When only the bioequivalence studies are conducted for the purpose of the following applications among the application categories of prescription drugs in “Approval Applications for Drugs” (PFSB Notification No. 1121-2 of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated November 21, 2014; hereinafter referred to as the “Director-General Notification”) (in this case, "bioequivalence studies" include pharmacodynamic studies to demonstrate therapeutic equivalence using pharmacological effects as

indices, in addition to studies to demonstrate equivalence by comparing bioavailability)

(8) Drugs in an additional dosage form (during the re-examination period)

(8-2) Drugs in an additional dosage form (not during the re-examination period)

(10) Other drugs (during the re-examination period)

(10-2) Other drugs ((10) related to changes in the manufacturing process of biological products, etc.)

(10-3) Other drugs (not during the re-examination period)

(10-4) Other drugs ((10-3) related to changes in the manufacturing process of biological products, etc.)

For over-the-counter drugs, the submission of annual reports is not required except for studies intended for application of drugs with new active ingredients in the application category (1) among the application categories of over-the-counter drugs in the Director-General Notification.

[2] When each study period is less than 1 year in studies for the development of generic drugs

[3] When each study period is less than 1 year in investigator-initiated clinical trials

The "each study period" in the above [2] and [3] refers to the period of actual conduct of a study, and may be considered as the study period entered in the column for study period (the remarks column if there is no column for study period) in various notifications (clinical trial plan notification, notification of changes in clinical trial plans, clinical trial discontinuation notification, or clinical trial completion notification).

<Submission of electronic media>

Q17

What file should be submitted when submitting an annual report in electronic media based on 1., (11), A, [1] of the Clinical Trial Periodic Report Director Notification?

A17

The files shall be in PDF format. It is desirable to prepare three separate files for Attached Form 1 and 2, and DSUR. If the files cannot be combined and there are files other than the following three files, the file name should be "Other_Test substance identification code_○ times (number of reports submitted)_Company name."

<How to name a file>

- Attached Form 1: Attached Form 1_Test substance identification code_○ times (number of reports submitted)_Company name
- Attached Form 2: Attached Form 2_Test substance identification code_○ times (number of reports submitted)_Company name
- DSUR: DSUR_Test substance identification code_○ times (number of reports submitted)_Company name

<Submission of electronic media>

Q18

Is it necessary to present the reporter information, etc. when submitting an annual report in electronic media based on 1., (11), A, [1] of Clinical Trial Periodic Report Director Notification?

A18

It is necessary. The following items shall be presented in the electronic media.

(1) Name of the reporter (for a corporation, its name) and the name, affiliation, and phone/fax number or e-mail address of the person in charge
(2) Test substance identification code, number of reports
(3) Date of report
(4) Receipt number (Prepare only the column without entering anything.)

Q19

How should the mandatory reporting period for annual reports on study drugs other than test drugs be considered?

A19

<If submission of clinical trial notification is required>

The period shall be from the date of submission of a notification for the clinical trial using the study drug concerned to the earliest date among the following.

- Date of submission of clinical trial completion notification or clinical trial discontinuation notification related to the clinical trial concerned
- Date of approval of the test drug of the clinical trial concerned
- Date of submission of development discontinuation notification for the test drug of the clinical trial concerned

<If submission of clinical trial notification is not required>

The period shall be from the start date of the study period entered in the protocol of the clinical trial using the study drug concerned to the earliest date among the following.

- The end date of the study period entered in the protocol of the clinical trial using the study drug concerned
- Date of approval of the test drug of the clinical trial concerned
- The date on which the Review Planning Division, Office of Review Management, PMDA is notified of planned discontinuation of development of the test drug of the clinical trial concerned in writing (in any format)

If the mandatory reporting period for study drugs other than the test drug ends before the end of the mandatory reporting period for the test drug, the information from the latest base date to the end date of the mandatory reporting period shall be included in the next annual report for the test drug.

Q20

In a clinical trial with multiple test drugs (e.g., Test drug A and Test drug B), study drugs other than the test drugs are also used. The information on the study drugs other than test drugs was planned to be reported together with Test drug A, and therefore the statement that "the information on the study drugs other than test drugs will be reported together with Test drug A" was entered in the remarks column of Attached Form 1 of the periodic report for Test drug B.

After that, if reporting of the information on the study drugs other than the test drugs together with Test drug B is desired for reasons such as discontinuation of development of Test drug A, what action should be taken?

A20

This circumstance should be explained in the remarks column of Attached Form 1 of the latest periodic reports of Test drug A and Test drug B so that the end date of the survey unit period for the reporting of the information on study drugs other than test drugs together with Test drug A and the start date of reporting of the information concerned together with Test drug B are clearly distinguished. In this regard, attention should be paid so that there will be no gap between the survey unit periods for the study drugs other than test drugs.

Q21

Is it acceptable to leave the column for "Information on study drugs other than the test drug" in Attached Form 1 of the Clinical Trial Periodic Report Director Notification blank when the clinical trial notification was submitted using the old form?

A21

It is acceptable to leave it blank.

Q22

What points should be considered when terminating withholding and resuming annual reports of cases of adverse reactions, etc. based on 1., (8), B of the Clinical Trial Periodic Report Director Notification?

Is it possible to submit the documents to be submitted in electronic media?

A22

Leave the column for the number of reports submitted in Attached Form 1 blank. The survey unit period should be from the day after the end of the survey unit period of the previous periodic report to the day before the latest base date. For DSUR, the report for one year up to the day before the latest base date may be attached.

In addition, the safety information collected while annual reports are withheld shall be reflected in the Investigator's Brochure and the protocol or summary of product application.

The documents can be submitted in electronic media. One electronic medium in which all documents to be submitted are saved in PDF format and one copy of the paper document of the notification of termination of withholding shall be submitted.

<How to name a file>

- Notification of termination of withholding: Notification of termination of withholding_Test substance identification code_ Company name
- Attached Form 1: Termination of withholding_Attached Form 1_Test substance identification code_Company name
- Attached Form 2: Termination of withholding_Attached Form 2_Test substance identification code_Company name
- DSUR: Termination of withholding_DSUR_Test substance identification code_Company name

The following items shall be presented in the electronic media.

(1) Name of the notifier of termination of withholding (for a corporation, its name) and the name, affiliation, and phone/fax number or e-mail address of the person in charge
(2) Test substance identification code
(3) Date of notification of termination of withholding
(4) Receipt number (Prepare only the column without entering anything.)

When submitting the notification of termination of withholding, contact Review Planning Division, Office of Review Management, PMDA in advance.

<Method of periodic reporting on study drugs other than test drugs>

Q23 In 1., (15) of the Clinical Trial Periodic Report Director Notification, it states that "the study drugs other than test drugs that were used in clinical trials with multiple test drugs may be reported together with one of the test drugs." How are they reported specifically?

A23

	Test substance identification code		Generic name
	Main test drug	Test drug	Study drugs other than test drugs
Clinical trial notification 1	A	-	X (hereinafter referred to as X1)
Clinical trial notification 2	A	B	Y (hereinafter referred to as Y2)
Clinical trial notification 3	C	B	Y (hereinafter referred to as Y3) Z (hereinafter referred to as Z3)

* For study drugs other than test drugs, the same alphabet means the same active ingredient.

Examples of clinical trials using multiple test drugs under one clinical trial notification are shown in the table above. Report as shown below.

Report X1 together with the periodic report on A.
Report Y2 together with the periodic report on A or B.
Report Y3 together with the periodic report on C or B.

Report Z3 together with the periodic report on C or B (even when Y3 is reported together with the periodic report on C, Z3 can be reported together with the periodic report on B).