PSB/PED Notification No. 1226-3
December 26, 2023

To: Directors of Prefectural Health Departments (Bureaus)

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

Partial Revision of "Points to Consider for Periodic Reporting of Cases of Adverse Reactions, etc. in Clinical Trials"

The points to consider for reporting suspected cases, etc. of adverse reactions or infections (hereinafter referred to as "cases of adverse reactions, etc.") related to the study drugs, etc. specified in Article 273, Paragraph 4 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; hereinafter referred to as the "Regulation") have 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 "Director Notification").

We have recently reviewed the handling of notifications by sponsors to investigators and the heads of medical institutions based on the provisions of Article 20, Paragraph 2 of Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs (Ministry of Health and Welfare Ordinance No. 28 of 1997) described in 3. Other in the note for Director Notification, and changed it as follows. Please be aware of this change and inform related businesses under your jurisdiction accordingly.

The revised Director Notification is as shown in the attachment, and will be applied from December 26, 2023. However, until February 29, 2024, the above notifications may be handled according to the previous rules under Director Notification before revision.

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.

Note

Corresponding part	New	Old
3.	3. Other It is acceptable to make notifications by sponsors to investigators and heads of medical institutions based on the provisions of Article 20, Paragraph 2 of the Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs (Ministry of Health and Welfare Ordinance No. 28 of 1997) within three months after the end of the survey unit period by attaching the Summary of Development Safety Update Report (Attached Form 1) and the List of Occurrence Status of Domestic Cases of Serious Adverse Reactions, etc. (Attached Form 2) to the attached reference form, "Annual Report of Development Safety Information." In this case, only the List of Occurrence Status of Domestic Cases of Serious Adverse Reactions, etc. (Attached Form 2) related to the test drug is required in principle. The investigator and head of medical institution shall check the Summary of Development Safety Update Report (Attached Form 1), and only when they find anything requiring the list related to the study drugs other than the test drug, the List of Occurrence Status of Domestic Cases of Serious Adverse reactions, etc. (Attached Form 2) for the study drug concerned should be submitted.	3. Other It is acceptable to make notifications by sponsors to investigators and heads of medical institutions based on the provisions of Article 20, Paragraph 2 of the Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs (Ministry of Health and Welfare Ordinance No. 28 of 1997) within three months after the end of the survey unit period by attaching the Summary of Development Safety Update Report (Attached Form 1) and the List of Occurrence Status of Domestic Cases of Serious Adverse Reactions, etc. (Attached Form 2) to the attached reference form, "Annual Report of Development Safety Information."

End of Document

Attachment

PSEHB/PED Notification No. 0831-14
August 31, 2020
[Partially revised] December 26, 2023

To: Directors of Prefectural Health Departments (Bureaus)

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

Points to Consider for Periodic Reporting of Cases of Adverse Reactions, etc. in Clinical Trials

The points to consider for reporting suspected cases, etc. of adverse reactions or infections (hereinafter referred to as "cases of adverse reactions, etc.") related to the study drugs, etc. specified in Article 273, Paragraph 4 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; hereinafter referred to as the "Regulation") (hereinafter referred to as "periodic reports") have been shown in "Points to Consider for Enforcement, etc. of Ministerial Ordinance for Partial Revision of the Ministerial Ordinance for Enforcement of the Pharmaceutical Affairs Act Related to Reporting of Adverse Reactions, etc. Related to Clinical Trials on Drugs" (PFSB/ELD Notification No. 1001005 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 1, 2008; hereinafter referred to as the "2008 Director Notification") and "Points to Consider for Enforcement of Ministerial Ordinance for Partial Revision of the Ministerial Ordinance for Enforcement of the Pharmaceutical Affairs Act, etc." (PFSB/ELD Notification No. 1228-11 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated December 28, 2012; hereinafter referred to as the "Periodic Report Old Director Notification").

With the enforcement of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 63 of 2019) and the Ministerial Ordinance on the Development of Related Ministerial Ordinances in Accordance with Enforcement of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ordinance No. 155 of Ministry of Health, Labour and Welfare in 2020), the following provisions have been established. Please be aware of them and inform related businesses under your jurisdiction accordingly. In association with this, the 2008 Director Notification and Periodic Report Old Director Notification will be abolished.

Please note that the periodic reports based on the ICH E2F guideline are reports for obtaining comprehensive safety information on the test drug every year, and should not be used as a means of providing new safety information.

Note

1. Article 273, Paragraph 4 of Regulation

For periodic reports made by the party that requested a clinical trial (hereinafter referred to as the "sponsor") based on the provisions of Article 273, Paragraph 4 of Regulation, cumulative reporting for each year (hereinafter referred to as the "annual report") is required. The forms, etc. shall be in accordance with the following (1) to (11). For sponsor-investigators (excluding the cases where a sponsor-investigator has conducted a clinical trial of a drug for which marketing approval has already been granted or a sponsor has already conducted a clinical trial of the test drug concerned), the "sponsor" should be read as the "sponsor-investigator."

(1) Forms

The annual report shall be submitted by the following A to C.

For study drugs other than test drugs, annual reports should be made as a whole for each test drug. For study drugs other than test drugs, the following C is not required.

A Summary of Development Safety Update Report (Attached Form 1)

B List of Occurrence Status of Domestic Cases of Serious Adverse Reactions, etc. (Attached Form 2)

C Development Safety Update Report (hereinafter referred to as "DSUR")

(2) Summary of Development Safety Update Report (Attached Form 1)

Refer to 1. of the attachment for detailed method of description.

(3) List of Occurrence Status of Domestic Cases of Serious Adverse Reactions, etc. (Attached Form 2)

Refer to 2. of the attachment for detailed method of description.

(4) DSUR

When preparing DSUR, follow "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) and refer to 3. of the attachment. If it is prepared in English, it is not necessary but acceptable to attach the Japanese version.

(5) Base date for reporting

The base date for reporting shall be as follows in principle, but when setting a base date for reporting other than the following is considered for a rational reason, the Review Planning Division, Office of Review Management, Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") shall be consulted in advance.

A For the survey unit period for annual reports, the date (month and day) on which the notification of a clinical trial plan for the test drug concerned was submitted or such a clinical trial was approved for the first time in Japan or abroad (hereinafter referred to as the "Development International Birth Date") is the base date for reporting for each year. If the Development International Birth Date is not the date on which a clinical trial notification for the test drug concerned was submitted for the first time in Japan, the initial report shall be made with the report prepared for the latest survey unit period after the notification of the clinical trial plan is submitted. If the test drug concerned is approved for manufacturing or marketing in Japan or overseas, the base date for reporting for the survey unit period can be set on the date (month and day) on which manufacturing or marketing is first approved in Japan or overseas (hereinafter referred to as the "International Birth Date").

When a notification of the clinical trial plan is not required, the start date of the implementation period written in the protocol shall be the base date for reporting.

B For study drugs other than the test drug, reports should be made with the same survey unit period for the test drug. If any study drug other than the test drug is newly added during the survey unit period of the test drug, the study drug should be included in the latest annual report to start reporting.

(6) Mandatory reporting period

A The mandatory reporting period for a test drug shall be from the date of the first submission of notification on the test drug concerned to its approval or to the submission of a development discontinuation notification. If submission of the clinical trial notification is not required, the mandatory reporting period shall be from the start date of the implementation period specified in the protocol for the test drug concerned to its approval or to the notification of planned discontinuation of development to the Review Planning Division, Office of Review Management, PMDA in writing (in any format).

B The mandatory reporting period for study drugs other than the test drug shall be from the date of submission of the notification for the clinical trial conducted using the study drug concerned to the submission of a clinical trial completion notification for the clinical trial concerned, to the approval of the test drug in the clinical trial concerned, or to the submission of a development discontinuation notification for the test drug concerned. If submission of the clinical trial notification is not required, the mandatory reporting period shall be from the start date of the implementation period specified in the protocol for the clinical trial using the study drug concerned to the completion date, to the approval of the test drug in the clinical trial concerned, or to the notification of planned discontinuation of development of the test drug concerned to the Review Planning Division, Office of Review Management, PMDA in writing (in any format).

(7) Timing of reporting

The annual report should be submitted within two months after the end of each survey unit period. If the deadline for reporting falls on a non-business day of PMDA, the next business day should be regarded as the deadline for reporting. The last periodic report after approval or submission of a development discontinuation notification shall be made within 2 months from the date of approval or submission of a development

discontinuation notification by A and B in (1) above. If two months is less than 60 days, it should be reported within 60 days.

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

(8) Long-term suspension of development, etc.

A If the development is expected to be suspended for a long time or it is expected to take a long time to prepare responses to inquiries after expert discussion while the approval application is reviewed, and annual reports will be withheld until the development is resumed or until responses to inquiries are submitted, the sponsor shall submit "Notification of Withholding of Reports of Adverse Reaction/Infection Cases Associated with the Investigational Product" (hereinafter referred to as "Notification of Withholding") to Review Planning Division, Office of Review Management, PMDA based on 8., (3), C., (b), [2] of "Partial Revision of 'Post-marketing Reports of Adverse Reactions, etc. and Reports of Adverse Reactions, etc. in Clinical Trials According to E2B (R3) Implementation Guide'" (PSEHB/PED Notification No. 0831-12, PSEHB/PSD Notification No. 0831-3 issued jointly by the Director of Pharmaceutical Evaluation Division and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020; hereinafter referred to as "Two Director Notification").

If the development is expected to be suspended for a long time and annual reports will be withheld until the development is resumed, sponsor-investigators shall submit the Notification of Withholding to the Review Planning Division, Office of Review Management, PMDA based on 2., (2), A of "Reports of Adverse Reactions, etc. in Clinical Trials by Sponsor-investigators" (PSEHB/PED Notification No. 0831-13 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 "Notification on Adverse Reaction Reports in Investigator-initiated Clinical Trials").

Efforts shall be made to collect safety information even while annual reports are withheld, and the information concerned shall be reflected in the Investigator's Brochure and the protocol or summary of product application when the development is resumed.

B When resuming annual reports of cases of adverse reactions, etc. with the resumption of development, the sponsor shall submit the "Notification of Termination of Withholding of Reports of Adverse Reaction/Infection Cases Associated with the Investigational Product" (hereinafter referred to as the "Notification of Termination of Withholding") to the Review Planning Division, Office of Review Management, PMDA based on 8., (3), C., (c) of the attachment of the Two Director Notification.

When resuming annual reports of cases of adverse reactions, etc. with the resumption of development, the sponsor-investigator shall submit the Notification of Termination of Withholding to the Review Planning Division, Office of Review Management, PMDA based on 2., (2), B of the Notification on Adverse Reaction Reports in Investigator-initiated Clinical Trials.

The 8., (3), C., (c), [3] of the attachment of the Two Director Notification and 2., (2), B, 3) of the Notification on Adverse Reaction Reports in Investigator-initiated Clinical Trials shall be based on the information in the annual report concerned.

The 8., (3), C., (c), [3] of the attachment of the Two Director Notification and 2., (2), B, 2) of the Notification on Adverse Reaction Reports in Investigator-initiated Clinical Trials shall be implemented by A to C in (1) above.

(9) In the case where multiple developments are ongoing

In principle, annual reports shall be made for each active ingredient. When multiple test drugs are concomitantly used, annual reports shall be made for each active ingredient of the test drugs.

If a clinical trial is conducted using another investigational ingredient code for the same active ingredient and it is considered appropriate to make annual reports for each investigational ingredient code, consult the Review Planning Division, Office of Review Management, PMDA in advance.

(10) In the case of joint development

When a drug is jointly developed by multiple parties, one annual report should be prepared wherever possible, and the representative should submit the report in joint names with co-developers of the drug.

When preparation of one annual report is impossible, describe the reason in the remarks column of Attached Form 1 and submit it for each co-developer. The same shall apply in the case where a sponsor-investigator conducts a multicenter clinical trial.

(11) Number of copies to be submitted and where to submit

A Number of copies to be submitted

[1] When CD-R or DVD-R (hereinafter referred to as “electronic media") is submitted

One electronic medium in which 1., (1), A to C are saved in PDF format, one copy of the paper document in 1., (1), A

[2] When paper documents are submitted

Two copies of the paper documents in 1., (1), A to C

B Where to submit

Reports shall be submitted to the Review Planning Division, Office of Review Management, PMDA directly by delivery in person or by postal mail.

2. Timing of application of this notification

This notification shall apply from September 1, 2020. However, in cases where clinical trial notifications were submitted as per previous rules 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) and “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), actions for study drugs other than the test drug are not required.

3. Other

It is acceptable to make notifications by sponsors to investigators and the heads of medical institutions based on the provisions of Article 20, Paragraph 2 of the Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs (Ministry of Health and Welfare Ordinance No. 28 of 1997) within three months after the end of the survey unit period by attaching the Summary of Development Safety Update Report (Attached Form 1) and the List of Occurrence Status of Domestic Cases of Serious Adverse Reactions, etc. (Attached Form 2) to the attached reference form, "Annual Report of Development Safety Information."

In this case, only the List of Occurrence Status of Domestic Cases of Serious Adverse Reactions, etc. (Attached Form 2) related to the test drug is required in principle. The investigator and head of medical institution shall check the Summary of Development Safety Update Report (Attached Form 1), and only when either of them requires anything related to the study drugs other than the test drug, the List of Occurrence Status of Domestic Cases of Serious Adverse Reactions, etc. (Attached Form 2) for the study drug concerned should be submitted.

(Attachment)

Points to Consider for Preparation of Annual Reports

1. Preparation of Summary of Development Safety Update Report (Attached Form 1)
For (1) to (14) below, information on the test drug shall be entered.

(1) In the column for “Investigational ingredient code,” enter the investigational ingredient code determined at the sponsor (no more than 20 alphanumeric characters). If there are multiple investigational ingredient codes for the same active ingredient, these should be listed.

(2) In the column for “Ingredient name,” enter the non-proprietary name (JAN or INN) (English name and Japanese name). If the non-proprietary name has not been determined, leave the column blank.

(3) In the column for “Brand name,” in the case of clinical trials intended for partial changes in approved product information for drugs that have already been approved for marketing in Japan (hereinafter referred to as “partial change clinical trials”), enter the brand name of the drug concerned. Leave the column blank if the clinical trial is not a partial change clinical trial.

(4) Fill out the column for “Content and dosage form” so that the content of the active ingredient per dosage form is clearly presented.

(5) In the column for “Date of initial notification,” enter the date on which the first clinical trial notification related to the same test substance identification code was submitted. If there are multiple test substance identification codes for the same active ingredient, fill out the column so that the date of the first clinical trial notification for each code is clearly shown.

(6) In the column for "Development International Birth Date,” enter the Development International Birth Date (month, day and year).

(7) In the column for “International Birth Date,” enter the International Birth Date (month, day and year). Leave the column blank if there is no International Birth Date.

(8) In the column of “Approval date,” enter the date on which the drug concerned was first approved in Japan in the case of a partial change clinical trial. Leave the column blank if the clinical trial is not a partial change clinical trial.

(9) In the column for "Number of reports,” enter the total number of submissions of the summary.

(10) In the column for “Proposed indications,” enter all the proposed indications of the test drug concerned.

(11) In the column for “Proposed dosage and administration,” enter all the proposed dosage and administration of the test drug concerned.

(12) In the column for “Survey unit period," enter the period during which cases of serious adverse reactions, etc. were accumulated for the summary concerned.

(13) In the column for “Development phase,” enter the development phase of the clinical trials included in the periodic reports concerned. If multiple clinical trials have been conducted for the same active ingredient, enter the development phase for each clinical trial. If a clinical trial has been conducted using a different test substance identification code for the same active ingredient, describe this situation.

Regarding a development phase, enter the development stage of the test drug concerned as in “Phase I,” “Phase II,” etc. in accordance with “General Considerations for Clinical Trials” (PMSB/ELD Notification No. 380 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare,

dated April 21, 1998). For bioequivalence studies, describe the fact that they are bioequivalence studies.

(14) In the column for "Approval status in major developed countries," if the approval has been granted in the United States, the United Kingdom, Germany, France, or the EU, enter each name of the country where the approval was granted and the year of approval, etc.

(15) In the column for "Information on study drugs other than the test drug," list the generic names presented in the clinical trial notifications, for the study drugs used in the clinical trials that are ongoing or completed during the survey period concerned. The study drugs other than test drugs that were used in clinical trials with multiple test drugs may be reported all together with one of the test drugs.

The use (comparator, concomitant drug, rescue drug, etc.) of the study drugs concerned in the clinical trials concerned should also be described in this column, if possible.

(16) In the column for "Occurrence status of cases of serious adverse reactions, etc.," state "as per attachment" and attach the List of Occurrence Status of Domestic Cases of Serious Adverse Reactions, etc. (Attached Form 2).

The method for accumulating cases of adverse reactions, etc. in Attached Form 2 (handling of blinded cases, etc.) shall also be clearly stated.

(17) 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.)," describe the accumulation and evaluation of cases of serious adverse reactions, etc. mainly in clinical trials conducted in Japan and overseas clinical studies during the survey unit period concerned and cases of serious adverse reactions, etc. collected since the Development International Birth Date; the findings from nonclinical studies that are important for the conduct of clinical trials; and sponsor's comments, etc. on post-marketing safety information, etc. that may have a significant impact on clinical trials in cases where the test drug is marketed in Japan or overseas. For the test drug, the description should be based on the content of DSUR (particularly the executive summary), and the status in Japan, sponsor's comments, etc. should be added. For study drugs other than the test drug, the sponsor's comments, etc. should be described based on the collected information, etc.

When not all the required information can be entered, it is acceptable to state "as per appendix" in the column concerned and attach an appendix.

The sponsor's opinion should include the following contents.

A The contents of new safety assurance measures taken by the sponsor and future safety measures should also be described based on individual cases of adverse reactions, etc. during the survey unit period concerned.

B Describe whether measures such as revision of the written information to be provided to subjects in clinical trials, revision of the protocols, revision of PRECAUTIONS, and revision of the summary of data (draft PRECAUTIONS, etc.) for approval application have been taken or are scheduled to be taken based on new important safety assurance measures taken by the sponsor during the survey unit period concerned, along with its reason.

C In the case of information from abroad, describe it in such a way that the actions taken by the overseas sponsor are clearly different from the actions taken by the sponsor in Japan.

D The presence or absence of new cases of adverse reactions, etc. considered important for the conduct of clinical trials that were obtained during the survey unit period concerned should be written.

E In light of safety information on the test drug concerned obtained up to the latest survey unit period, the presence or absence of changes that are important for the conduct of clinical trials (causal relationship, occurrence status, outcome, etc.) should be written.

F Make evaluations based on the route of administration, dosage form, patient background (children, elderly, etc.), dose/treatment duration, relationship with the primary disease, etc. and enter the summary of the evaluations.

(18) "Remarks" column

A Enter the name and contact information of the person in charge.

B If the base date for reporting has been changed, describe the reason for the change.

C If the annual report concerned is the final report because of approval or discontinuation of development, enter the approval date or date of discontinuation of development.

D In the final report, the presence or absence of clinical studies ongoing in major developed countries should be specified.

E In the case of withholding annual reports, when terminating withholding and resuming them, enter the submission date of the notification of termination of withholding to the Review Planning Division, Office of Review Management, PMDA in the first report after the resumption of development.

F If the information on the study drugs other than test drugs that were used in clinical trials with multiple test drugs is reported together in an annual report of not the test drug concerned, but another test drug, indicate which test drug is selected to report the information on the study drugs concerned together.

G Describe other items warranting special mention, if any.

2. List of Occurrence Status of Domestic Cases of Serious Adverse Reactions, etc. (Attached Form 2)

Prepare the list for each study drug. For study drugs other than the test drug, it is acceptable to prepare the list for the clinical trials that are ongoing or completed during the survey period concerned.

(1) Describe the cases of serious adverse reactions, etc. reported from clinical trials conducted in Japan on or after the date of the first clinical trial notification for the test drug concerned in Japan. In the "Remarks" column, write what is included in the list where necessary (e.g., "The test drug concerned has been marketed for more than several years after it was approved, and the number, etc. of cases of serious adverse reactions, etc. from the clinical trials related to approved indications are excluded from the list.").

(2) In the column for "Code/name of study drug," enter the test substance identification code for the test drug, and the generic name and category information for study drugs other than the test drug.

(3) In the column for "Type of case of adverse reaction, etc.," select and enter the appropriate Preferred Term for each System Organ Class based on the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J). The same version of MedDRA/J should be used during the survey unit period concerned.

(4) For the column of "Number of cases of adverse reactions, etc. by type," tabulation by type of adverse reactions, etc. shall be performed using the number of subjects for the System Organ Classes, and using the number of events for the Preferred Terms. If multiple

cases of adverse reactions, etc. occurred in the same patient, each case of adverse reaction, etc. subject to reporting should be counted as one.

(5) As the approximate cumulative number of subjects, enter the total of the number of subjects enrolled in ongoing clinical trials and the number of subjects in completed clinical trials related to the study drug concerned in Japan. For study drugs other than the test drug, however, it is acceptable to enter the number of subjects enrolled in the clinical trials that are ongoing or completed during the survey period concerned as the approximate cumulative number of subjects.

3. Preparation of DSUR

(1) Reference safety information

The reference safety information is the Investigator's Brochure. However, the Investigator's Brochure used as the reference safety information may be different from that used in clinical trials conducted in Japan, when, for example, a DSUR prepared by an overseas sponsor is used for submission. When the reference safety information for DSUR is different from the Investigator's Brochure used in Japan (e.g., the content of the reminder in the guidance for investigators, etc. in the Investigator's Brochure is different because of different dosage forms/indications under development in Japan and abroad), describe this in the summary of the Development Safety Update Report or the appendix to the summary.

(2) Status of clinical trials that are ongoing or completed during the survey period

Describe the status of clinical studies conducted by the sponsor, in principle. When information on clinical studies conducted by other sponsors is obtained, describe in "8. Significant findings in clinical studies during survey period" as necessary.

(3) Estimated cumulative number of users

In principle, the estimated cumulative number of users in clinical studies conducted by the sponsor should be entered. When it is difficult to calculate the estimated cumulative number of users based on the Development International Birth Date, etc. (e.g. when the test drug concerned has been marketed for at least several years after it was approved), describe how the presented number was calculated, or the summary, etc. of missing data.

(4) Data in line lists and summary tables

In DSURs prepared by overseas sponsors, etc., the criteria for adverse events to be included in line lists and summary tables may differ if handling of specific adverse events is different in Japan and abroad (e.g., handling of adverse events specified in the protocol as those not subject to special collection and safety database registration, adverse events corresponding to efficacy endpoints, etc.). In this case, if any safety information of particular concern is found in the information separately collected in Japan, describe this in the summary of the Development Safety Update Report.

(5) Literature references

For new significant safety information based on literature, etc., copies of the original literature, abstracts of academic meetings, etc. are to be attached along with research reports and reports on measures taken. However, when submitting a DSUR to PMDA, it is not necessary to attach copies of literature/abstracts of academic meetings, etc. that have already been submitted to PMDA.

(6) Other

When it is difficult for the sponsor to obtain the information that should be entered in the items for reporting for some reasons (e.g., sponsor-investigators may find it difficult to obtain the information on quality issues of the test drug that affect the

conduct of clinical trials, overseas post-marketing spontaneous reports, research reports, nonclinical study data, etc.), describe this in the DSUR.