Administrative Notice
August 10, 2023

To: Pharmaceutical Affairs Section, Prefectural Health Department (Bureau)

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

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

Revision of Q&A on Post-marketing Reports of Adverse Reactions, etc. and Reports of Adverse Reactions, etc. in Clinical Trials According to E2B (R3) Implementation Guide

Questions and answers (Q&A) on "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) were shown in "Revision of Q&A on Post-marketing Reports of Adverse Reactions, etc. and Reports of Adverse Reactions, etc. in Clinical Trials According to E2B (R3) Implementation Guide" (Administrative Notice issued jointly by the Pharmaceutical Evaluation Division and the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated June 24, 2022; hereinafter referred to as "Old Administrative Notice").

With the issuance, etc. of "Partial Revision of 'Guidelines on Provision of Dear Healthcare Professional Letters of Emergent Safety Communications, etc.'" (PSEHB/PSD Notification No. 0810-2 of the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 10, 2023), the contents of Q&A have been partially revised, and other necessary revisions have been implemented as shown in Appendix 1 and newly summarized in Appendix 2. Please be aware of these revisions and inform related businesses, etc. under your jurisdiction of them as references for operations.

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

(Appendix 1)

○ Comparison table of new and old administrative notices

New administrative notice: "Revision of Q&A on Post-marketing Reports of Adverse Reactions, etc. and Reports of Adverse Reactions, etc. in Clinical Trials According to E2B (R3) Implementation Guide" (Administrative Notice issued jointly by the Pharmaceutical Evaluation Division and the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 10, 2023)

Old Administrative Notice: "Revision of Q&A on Post-marketing Reports of Adverse Reactions, etc. and Reports of Adverse Reactions, etc. in Clinical Trials According to E2B (R3) Implementation Guide" (Administrative Notice issued jointly by the Pharmaceutical Evaluation Division and the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated June 24, 2022)

(The underlined parts in red are revised.)

New administrative notice	Old administrative notice
Q1 to Q17 (Omitted)	Q1 to Q17 (Omitted)
Q18: [Post-marketing] In Note 2. (2) in PMSB/SD Notification No. 25 of the Safety Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated March 11, 1998, "Thorough Implementation of Safety Measures for Drugs," it is stated that "If the information on an event similar to the adverse reaction that is to be newly listed in association with revision of the package insert is obtained before the completion of information transmission to medical institutions, etc. after the revision of the package insert, the event shall be handled as 'an adverse reaction that cannot be expected from PRECAUTIONS' and reported within 15 days." When is the information transmission to medical institutions, etc. considered to be completed?	Q18 [Post-marketing] In Note 2. (2) in PMSB/SD Notification No. 25 of the Safety Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated March 11, 1998, "Thorough Implementation of Safety Measures for Drugs," it is stated that "If the information on an event similar to the adverse reaction that is to be newly listed in association with revision of the package insert is obtained before the completion of information transmission to medical institutions, etc. after the revision of the package insert, the event shall be handled as 'an adverse reaction that cannot be expected from PRECAUTIONS' and reported within 15 days." When is the information transmission to medical institutions, etc. considered to be completed?
A18: [Post-marketing] It shall be the date on which the information transmission determined by the marketing authorization holder is completed.	A18: [Post-marketing] It shall be the date on which the information transmission by the marketing authorization holder is completed or the date on which the DRUG SAFETY UPDATE (DSU) is distributed to medical institutions, whichever comes first.
Q19 (Omitted)	Q19 (Omitted)

Q20: [Clinical trial] When additional medically important information is obtained and an additional report is to be submitted for an already reported case, is it correct to determine the date on which additional information was obtained as the base date for reckoning the legal reporting deadline?	Q20: [Clinical trial] When additional medically important information is obtained and an additional report is to be submitted for an already reported case, is it correct to determine the date on which additional information was obtained as the base date for reckoning the legal reporting deadline?
A20: [Clinical trial] It is correct. An additional report should be submitted within the deadline determined by reckoning the date on which additional information was obtained as the base date. For example, if additional information subject to reporting within 7 days is obtained for a case that has already been reported within 15 days, an additional report should be submitted within 7 days. If additional information subject to reporting is obtained for a case that has already been reported within 7 days, an additional report should be submitted within 15 days. In this case, too, the reporting category shall be indicated as 7 days and "Yes" shall be entered for "C.1.7 Does This Case Fulfill the Local Criteria for an Expedited Report?" However, when additional information that should be reported within 7 days (new adverse event, change of adverse event name, change of seriousness or seriousness criteria) is newly obtained, the additional report should be submitted within 7 days.	A20: [Clinical trial] It is correct. An additional report should be submitted within the deadline determined by reckoning the date on which additional information was obtained as the base date. For example, if additional information subject to reporting within 7 days is obtained for a case that has already been reported within 15 days, an additional report should be submitted within 7 days. If additional information subject to reporting is obtained for a case that has already been reported within 7 days, an additional report should be submitted within 7 days unless the reporting deadline is changed to within 15 days based on the additional information.
Q21 to Q44 (Omitted)	Q21 to Q44 (Omitted)
Q45: [Post-marketing] [Clinical trial] Is the use of characters with an umlaut mark acceptable for the input type, "TXT"?	Q45: [Post-marketing] [Clinical trial] Is the use of characters with an umlaut mark acceptable for the input type, "TXT"?
A45: [Post-marketing] [Clinical trial]	A45: [Post-marketing] [Clinical trial]

Characters with an umlaut mark, etc. can be accepted as long as they are available in UTF-8. However, it is desirable not to use characters with an umlaut mark to state cases in Japan. Letter types such as “<” or “>” that are not permitted in the XML messages cannot be used. Q46 to Q59 (Omitted) Q60: [Post-marketing] [Clinical trial] When a case identical to a case reported in a “report of adverse reactions, etc. in clinical trials” is reported as a “post-marketing report of adverse reactions, etc.,” is it always necessary to provide the identifier in each report in “C.1.8.1 Worldwide Unique Case Identification Number” and “C.1.10.r Identification Number of the Report Linked to This Report”? A60: [Post-marketing] [Clinical trial] “C.1.8.1” should be the same identifier in the “post-marketing report of adverse reactions, etc.” and the “report of adverse reactions, etc. in clinical trials,” and the identifier in each report should be entered in “C.1.10.r” where possible. In addition, in “J2.11 Other Reference Matters, etc.,” it shall be stated that the “report of adverse reactions, etc. in clinical trials” (or the “post-marketing report of adverse reactions, etc.”) has already been submitted or is scheduled to be submitted, and if it has already been submitted, “J2.1 Identification Number” of the report concerned shall also be entered. Q61 to Q98 (Omitted)	Characters with an umlaut mark, etc. can be accepted as long as they are available in UTF-8. However, it is desirable not to use characters with an umlaut mark to state cases in Japan. Letter types such as “<” or [>] that are not permitted in the XML messages cannot be used. Q46 to Q59 (Omitted) Q600: [Post-marketing] [Clinical trial] When a case identical to a case reported in a “report of adverse reactions, etc. in clinical trials” is reported as a “post-marketing report of adverse reactions, etc.,” is it always necessary to provide the identifier in each report in “C.1.8.1 Worldwide Unique Case Identification Number” and “C.1.10.r Identification Number of the Report Linked to This Report”? A600: [Post-marketing] [Clinical trial] “C.1.8.1” should be the same identifier in the “post-marketing report of adverse reactions, etc.” and the “report of adverse reactions, etc. in clinical trials,” and the identifier in each report should be entered in “C.1.10.r” where possible. In addition, in “J2.11 Other Reference Matters, etc.,” it shall be stated that the “report of adverse reactions, etc. in clinical trials” (or the “post-marketing report of adverse reactions, etc.”) has already been submitted or is scheduled to be submitted, and if it has already been submitted, “J2.1 Identification Number” of the report concerned shall also be entered. Q61 to Q98 (Omitted)

Q99: [Post-marketing] [Clinical trial] Regarding adverse reactions in Japan that occurred around the approval date, how should it be judged whether they should be reported as “reports of adverse reactions, etc. in clinical trials” or “post-marketing reports of adverse reactions, etc.”? A99: [Post-marketing] [Clinical trial] It should be judged based on the approval status of the product concerned/test drug in Japan at the date and time of onset of the adverse reaction. (1) Adverse reactions that occurred before the approval date should be reported as “reports of adverse reactions, etc. in clinical trials” based on provisions of Article 273 of the Regulation. (2) Additional information on adverse reactions that occurred before the approval date should be reported in additional reports as “reports of adverse reactions, etc. in clinical trials.” In this regard, enter “8 = Other” in “J2.13.r.3 Development Phase,” and the phrase, “After approval,” and the “brand name” in “J2.11 Other Reference Matters, etc.” (3) Adverse reactions that occurred on or after the approval date should be reported as “post-marketing reports of adverse reactions, etc.” based on the provisions of Article 228-20 of the Regulation. Moreover, information on other adverse reactions which newly occurred on or after the approval date in patients who were reported in “reports of adverse reactions, etc. in clinical trials” before the approval date should be reported in initial reports also as “post-marketing reports of adverse reactions, etc.” In these reports, necessary information shall be entered with reference to Q&A 60 and 61. If an additional report in (2) and a report of another adverse reaction that newly occurred on or after the approval date are to be submitted at the same time, they may be reported together as a “post-marketing report of adverse reactions, etc.”	Q99: [Post-marketing] [Clinical trial] Regarding adverse reactions in Japan that occurred around the approval date, how should it be judged whether they should be reported as "reports of adverse reactions, etc. in clinical trials" or “post-marketing reports of adverse reactions, etc."? A99: [Post-marketing] [Clinical trial] It should be judged based on the approval status of the product concerned/test drug in Japan at the date and time of onset of the adverse reaction. (1) Adverse reactions that occurred before the approval date should be reported as “reports of adverse reactions, etc. in clinical trials” based on provisions of Article 273 of the Regulation. (2) Additional information on adverse reactions that occurred before the approval date should be reported in additional reports as “reports of adverse reactions, etc. in clinical trials.” In this regard, enter “8 = Other” in “J2.13.r.3 Development phase,” and the phrase, “After approval,” and the “brand name” in “J2.11 Other reference matters, etc.” (3) Adverse reactions that occurred on or after the approval date should be reported as “post-marketing reports of adverse reactions, etc.” based on the provisions of Article 228-20 of the Regulation. Moreover, information on other adverse reactions which newly occurred on or after the approval date in patients who were reported in “reports of adverse reactions, etc. in clinical trials” before the approval date should be reported in initial reports also as “post-marketing reports of adverse reactions, etc.” In these reports, necessary information shall be entered with reference to Q&A 62 and 63. If an additional report in (2) and a report of another adverse reaction that newly occurred on or after the approval date are to be submitted at the same time, they may be reported together as a “post-marketing report of adverse reactions, etc.”
Q100: [Post-marketing] [Clinical trial] Regarding overseas adverse reactions that occurred around the approval	Q100: [Post-marketing] [Clinical trial] Regarding overseas adverse reactions that occurred around the approval

date, how should it be judged whether they should be reported as “reports of adverse reactions, etc. in clinical trials” or “post-marketing reports of adverse reactions, etc.”?	date, how should it be judged whether they should be reported as “reports of adverse reactions, etc. in clinical trials” or “post-marketing reports of adverse reactions, etc.”?
A100: [Post-marketing] [Clinical trial] It should be judged based on the approval status of the product concerned in Japan at the time when the information is obtained. (1) If the initial information is obtained before the approval date, it should be reported as a “report of adverse reactions, etc. in clinical trials” based on provisions of Article 273 of the Regulation. If additional information on the case concerned is obtained on or after the approval date, the initial report shall be newly made as a “post-marketing report of adverse reactions, etc.” based on provisions of Article 228-20 of the Regulation. In this regard, enter necessary information referring to Q&A 60 and 61. (2) If the first information is obtained on or after the approval date, the initial report shall be made as a “post-marketing report of adverse reactions, etc.”	A100: [Post-marketing] [Clinical trial] It should be judged based on the approval status of the product concerned in Japan at the time when the information is obtained. (1) If the initial information is obtained before the approval date, it should be reported as a “report of adverse reactions, etc. in clinical trials” based on the provisions of Article 273 of the Regulation. If additional information on the case concerned is obtained on or after the approval date, the initial report shall be newly made as a “post-marketing report of adverse reactions, etc.” based on provisions of Article 228-20 of the Regulation. In this regard, enter necessary information referring to Q&A 62 and 63. (2) If the first information is obtained on or after the approval date, the initial report shall be made as a “post-marketing report of adverse reactions, etc.”
Q101 to Q110 (Omitted)	Q101 to Q110 (Omitted)
Q111: [Post-marketing] [Clinical trial] How should the elements other than “E.i.3.2 Seriousness Criteria at Event Level” shown in the above Q110 for which the value allowed is specified as “code value,” “true,” or “false” be written in the case of paper-based reporting?	Q111: [Post-marketing] [Clinical trial] How should the elements other than "E.i.3.2 Seriousness Criteria at Event Level” shown in the above Q112 for which the value allowed is specified as “code value,” “true,” or “false” be written in the case of paper-based reporting?

A111: [Post-marketing] [Clinical trial] Instead of entering “code value,” “true,” or “false” as they are, write the elements so that their contents are clearly understood from the report without referring to the code table, etc. Q112 to Q135 (Omitted) Q136: [Post-marketing] [Clinical trial] If information to be reported is obtained around the approval date, how should it be judged whether to report the information as a “clinical trial research/foreign corrective action report” or as a “post-marketing research/foreign corrective action report”? A136: [Post-marketing] [Clinical trial] It should be judged based on the approval status of the product concerned in Japan at the time when the information is obtained. (1) If the initial information is obtained before the approval date, it should be reported as a “clinical trial research/foreign corrective action report” based on the provisions of Article 273 of the Regulation. If additional information on the report concerned is obtained on or after the approval date, the initial report shall be newly made as a “post-marketing research/foreign corrective action report” based on provisions of Article 228-20 of the Regulation. In this regard, enter necessary information referring to Q&A 137 and 138. (2) If the first information is obtained on or after the approval date, the initial report shall be made as a “post-marketing research/foreign corrective action report.”	A111: [Post-marketing] [Clinical trial] Instead of entering “code value,” “true,” or “false” as they are, write the elements so that their contents are clearly understood from the report without referring to the code table, etc. Q112 to Q135 (Omitted) Q136: [Post-marketing] [Clinical trial] If information to be reported is obtained around the approval date, how should it be judged whether to report the information as a “clinical trial research/foreign corrective action report” or as a “post-marketing research/foreign corrective action report”? A136: [Post-marketing] [Clinical trial] It should be judged based on the approval status of the product concerned in Japan at the time when the information is obtained. (1) If the initial information is obtained before the approval date, it should be reported as a “clinical trial research/foreign corrective action report” based on the provisions of Article 273 of the Regulation. If additional information on the report concerned is obtained on or after the approval date, the initial report shall be newly made as a “post-marketing research/foreign corrective action report” based on provisions of Article 228-20 of the Regulation. In this regard, enter necessary information referring to Q&A 139 and 140. (2) If the first information is obtained on or after the approval date, the initial report shall be made as a “post-marketing research/foreign corrective action report.”
Q137 to Q169 (Omitted)	Q137 to Q169 (Omitted)

Appendix 2

Q&A on Post-marketing Reports of Adverse Reactions, etc. and Reports of Adverse Reactions, etc. in Clinical Trials According to E2B (R3) Implementation Guide

August 10, 2023

TABLE OF CONTENTS

[Abbreviations used]

Act: Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960)

Regulation: 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)

Post-marketing Director-General Notification: PFSB Notification No. 1002-20 of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 2, 2014, "Reporting of Adverse Reactions, etc. to Drugs, etc."

Clinical Trial Director-General Notification: PSEHB Notification No. 0831-8 of the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020, "Reports of Adverse Reactions, etc. in Clinical Trials to Pharmaceuticals and Medical Devices Agency"

E2B (R3) Two Director Notification: 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, "Post-marketing Reports of Adverse Reactions, etc. and Reports of Adverse Reactions, etc. in Clinical Trials According to E2B (R3) Implementation Guide"

E2B (R2) Two Director Notification: PFSB/ELD Notification No. 0331022, PFSB/SD Notification No. 0331009 issued jointly by the Director of Evaluation and Licensing Division and the Director of Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 31, 2006, "Post-marketing Reports of Adverse Reactions, etc. and Reports of Adverse Reactions, etc. in Clinical Trials" (abolished)

E2B (R3) Five Director Notification: PMDA/ORM Notification No. 0831001, PMDA/OIMS Notification No. 0831003, PMDA/OPI Notification No. 0831001, PMDA/OPII Notification No. 0831001, PMDA/OMQVMD Notification No. 0831001 issued jointly by the Director of Office of Review Management, the Director of Office of Informatics and Management for Safety, the Director of Office of Pharmacovigilance I, the Director of Office of Pharmacovigilance II, and the Director of Office of Manufacturing Quality and Vigilance for Medical Devices, Pharmaceuticals and Medical Devices Agency, dated August 31, 2020, "Points to Consider for Post-marketing Reports of Adverse Reactions, etc. and Reports of Adverse Reactions, etc. in Clinical Trials According to E2B (R3) Implementation Guide"

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

E2B (R3) Implementation Guide: PSEHB/PED Notification No. 0315-6, PSEHB/PSD Notification No. 0315-1 issued jointly by the Director of Pharmaceutical Evaluation Division and the Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 15, 2017, "Corrections, etc. of Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs)"

E2B (R3) ICH Q&A: Administrative Notice issued jointly by the Pharmaceutical Evaluation Division and the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated September 26, 2019, "Electronic Transmission of Individual Case Safety Reports (ICSRs) Questions and Answers"

E2D Guideline: PFSB/SD Notification No. 0328007 of the Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 28, 2005, "Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting"

Post-marketing reports of adverse reactions, etc.: Reports of adverse reactions, etc. specified in Article 68-10, Paragraph 1 of the Act

Reporting of adverse reactions, etc. in clinical trials: Reports of adverse reactions, etc. specified in Article 80-2, Paragraph 6 of the Act

PMDA: Pharmaceuticals and Medical Devices Agency

Electronic reporting: Reporting via electronic data processing systems

Reporting by CD, etc.: Reporting by submitting the CD-R (ROM) or DVD-R (ROM) in which the items listed in the attached forms of Post-marketing Director-General Notification or the attached forms of Clinical Trial Director-General Notification are recorded and a document describing necessary information such as name and address of the reporter and the date of reporting specified in the Post-marketing Director-General Notification or Clinical Trial Director-General Notification

Paper-based reporting: Reporting by submitting a report describing necessary information specified in the attached forms of Post-marketing Director-General Notification and the attached forms of Clinical Trial Director-General Notification, and CD-R (ROM) or DVD-R (ROM) in which items listed in Appendix 1, "Data Elements for Management of Systems of the Ministry of Health, Labour and Welfare," and Appendix 2, "Data Elements in Individual Case Safety Reports," of E2B (R3) Two Director Notification are recorded in XML format in compliance with E2B (R3) Implementation Guide

Immediate reports: Reports corresponding to 2 (1) [2] of the attachment of Post-marketing Director-General Notification

ICSR files: Electronic files in which E2B data elements and J data elements are recorded in XML format

Old reporting criteria: Regulations for reporting of adverse reactions, etc. or reporting of adverse reactions, etc. related to clinical trials on drugs in the Ministerial Ordinance for Enforcement of the Pharmaceutical Affairs Act before the revision by the Ministerial Ordinance for Partial Revision of the Ministerial Ordinance for Enforcement of the Pharmaceutical Affairs Act (Ordinance No. 30 of the Ministry of Health, Labour and Welfare, 2005)

1. Reports of adverse reactions, etc. and infections

(1) Reporting target

Q1: [Post-marketing] [Clinical trial]
What is the scope of "events suspected to be adverse reactions"?
Are cases for which a causal relationship cannot be ruled out or cases for which a causal relationship is unknown subject to reporting?

A1: [Post-marketing] [Clinical trial]

In ICH, etc., an adverse drug reaction to be reported is defined as "an adverse event for which a causal relationship with the drug cannot be ruled out." In Japan, information is being collected practically within that scope.

The "events suspected to be adverse reactions" are events other than those for which a causal relationship can be ruled out. The "events for which a causal relationship is unknown" are also subject to reporting.

Q2: [Post-marketing] [Clinical trial]
Who determines "events suspected to be adverse reactions"?

A2: [Post-marketing] [Clinical trial]

The sender is responsible for judging it based on the contents of evaluation of the causal relationship provided as information by the reporter. Events other than those for which the sender and all reporters have judged that "causal relationship can be ruled out" should be reported. If the reporters include a "lawyer" or "consumer or other non-healthcare professional," as well as a "physician," "pharmacist," or "other healthcare professional," a judgement can be made that all the reporters have ruled out the causal relationship when all the reporters who are either "physician," "pharmacist," or "other healthcare professional" have ruled out the causal relationship.

Q3: [Post-marketing]
Should cases requiring hospitalization or prolongation of hospitalization due to treatment of adverse reactions be considered serious even if they are determined by the reporter to be obviously non-serious?

A3: [Post-marketing]

These cases should be handled as serious cases.

Q4: [Post-marketing] [Clinical trial]
Should a suspected infection due to viral contamination which can only be detected by a currently and incompletely recognized test be reported even if viral contamination is negative when tested using a currently recognized test?

A4: [Post-marketing] [Clinical trial]

It needs to be reported. Infections suspected to have been caused by use of drugs must be reported whether or not the testing method has been established.

Q5: [Post-marketing]
Is reporting of adverse reactions, etc. necessary for adverse reactions caused by defective products?

A5: [Post-marketing]
Reporting of adverse reactions, etc. is necessary even if an adverse reaction has been caused by a defective product.

Q6: [Post-marketing]
Are cases of health hazards that occurred in the use that is obviously not for medical purposes such as treatment of diseases (e.g., suicide, crime, accidental ingestion by infants) subject to reporting?

A6: [Post-marketing]
These cases are not subject to reporting based on the provisions of Article 228-20 of the Regulation.

Q7: [Post-marketing]
It is stated in the Post-marketing Director-General Notification that "the cases that need to be reported urgently to the government at least in the country where they occurred should be reported." What points should be noted specifically?

A7: [Post-marketing]
For a certain drug marketed by a Japanese corporation in Japan and by a partner company, etc. in foreign countries, it should be noted that, if the partner company, etc. urgently reports a case of an adverse reaction to the government of the country where the case has occurred and the adverse reaction concerned cannot be predicted from the necessary precautions, etc. in Japan, the Japanese corporation should also consider the case as unknown/serious and report it.

Q8: [Post-marketing]
What are drugs that are used overseas and are subject to reporting because they are considered to have the same ingredients as those of the drugs concerned (approved in Japan)?

A8: [Post-marketing]

(1) If the drugs have the same ingredients, they are subject to reporting even if their dosage and administration, indications, or other active ingredients, etc. contained are not the same.
(2) If the sender has obtained marketing approval of multiple drug products containing the same ingredients in Japan and learned any overseas case of an adverse reaction or infection associated with the relevant active ingredient, the sender should report it as a case associated with the drug products considered relatively more appropriate among those for which the sender has obtained marketing approval in Japan in light of the reason for the use of the drug in the case, dosage and administration, other active ingredients contained, etc., thereby preventing omission in reporting.
(3) The information on adverse reactions, etc. that are serious and cannot be expected from necessary precautions, etc. is subject to reporting, when the information is about the drug with the same ingredients; this applies to the products of overseas partner companies and also those that are not the products of these partner companies.

Q9: [Post-marketing] [Clinical trial]
Should abortion associated with occurrence of malformation, etc. considered to have been caused by a drug or a study drug be reported as a parent-child/fetus report?

A9: [Post-marketing] [Clinical trial]
It should be reported as a parent-child/fetus report.

Q10: [Clinical trial]
Can the hospitalization (for scheduled surgeries, tests, etc.) only for the purpose of performing therapies or tests scheduled before the study during the study be excluded from reporting?

A10: [Clinical trial]
It may be excluded.

Q11: [Post-marketing]
Is an infection report necessary when a physician reports the following?
[1] Viral hepatitis due to blood products
[2] Sepsis associated with agranulocytosis
[3] Microbial substitution resulting from antibiotic use
[4] Aseptic meningitis associated with vaccination
[5] MRSA (methicillin-resistant Staphylococcus aureus) infection during treatment with antibiotics
[6] Emerging infectious diseases that occurred during the use of drugs, etc.

A11: [Post-marketing]
(1) [1] requires an infection report.
(2) Reporting as adverse reactions has been required for [2] to [4]. These cases should continue to be reported in the same manner.
(3) [5] does not require a case report, but Office of Pharmacovigilance I or Office of Pharmacovigilance II of PMDA should be consulted individually as to whether the findings related to changes, etc. in the resistance mechanism or the tendency toward emergence of the bacteria resistant to the antibiotics in association with their use should be handled as research reports.
(4) [6] requires infection reports. Regardless of whether the case is found in Japan or overseas, detailed information on the patient's symptoms, etc. should be investigated, and the rationale for diagnosis should be clarified.

If such a case occurs, Office of Pharmacovigilance I or Office of Pharmacovigilance II (Medical Device Safety Division, Office of Manufacturing Quality and Vigilance for Medical Devices for in vitro diagnostics) of PMDA should be consulted individually.

Q12: [Post-marketing]
Occurrence of an adverse event was found in the investigation using medical information databases such as MID-NET, but there is no correspondence table and it is not possible to trace back to the original medical information. In this case, is it necessary to make a report of adverse reactions, etc. or infections?

A12: [Post-marketing]

If a medical information database does not have a correspondence table enabling cross-checking of the original medical information, the information is provided on the premise that it is not traced back to the original medical information, and therefore it is acceptable not to investigate additional information. For information obtained from a medical information database without a correspondence table, reporting of each individual case of adverse reaction/infection is not necessary.

Q13: [Clinical trial]

For test drugs and study drugs other than test drugs, how should the cases requiring reporting and the reporting deadlines be considered?

A13: [Clinical trial]

For test drugs and study drugs other than test drugs, cases requiring reporting and the reporting deadlines are as follows.

If the test drug corresponds to "other than partial changes," it should be responded to in accordance with the table for "other than partial changes." If the test drug corresponds to "partial changes," it should be responded to in accordance with the table for "partial changes."

For study drugs other than test drugs, if there is any test drug classified as “other than partial changes" in the notification, they should be responded to in accordance with the table for “other than partial changes." If all the test drugs in the notification are classified as “partial changes,” they should be responded to in accordance with the table for “partial changes."

<Cases in clinical trials in Japan>

	Expectedness	Seriousness	Other than partial changes	Partial changes*
Test drug	Unknown	Death/life-threatening	7 days	7 days
		Other seriousness	15 days	15 days
	Known	Death/life-threatening	15 days	15 days
		Other seriousness	Not required	Not required
Study drugs other than test drugs	Unknown	Death/life-threatening	7 days	7 days
		Other seriousness	15 days	15 days
	Known	Death/life-threatening	15 days	15 days
		Other seriousness	Not required	Not required

<Cases in overseas clinical studies>

	Expectedness	Seriousness	When the test drug concerned was used in an overseas clinical study		When the test drug concerned was not used in any overseas clinical study
			Other than partial changes	Partial changes*	
Test drug	Unknown	Death/life-threatening	7 days	Not required	-

		Other seriousness	15 days	Not required	-
	Known	Death/life-threatening	15 days	Not required	-
		Other seriousness	Not required	Not required	-
Study drugs other than test drugs	Unknown	Death/life-threatening	7 days	Not required	Not required
		Other seriousness	15 days	Not required	Not required
	Known	Death/life-threatening	15 days	Not required	Not required
		Other seriousness	Not required	Not required	Not required

<Cases in overseas use (excluding use in clinical studies)>

	Expectedness	Seriousness	Other than partial changes	Partial changes*
Test drug	Unknown	Death/life-threatening	7 days	Not required
		Other seriousness	15 days	Not required
	Known	Death/life-threatening	15 days	Not required
		Other seriousness	Not required	Not required
Study drugs other than test drugs	Unknown	Death/life-threatening	Not required	Not required
		Other seriousness	Not required	Not required
	Known	Death/life-threatening	Not required	Not required
		Other seriousness	Not required	Not required

* Limited to clinical trials used for application for approval of partial changes in approved product information related to addition, change, or deletion of dosage, administration, or indications.

Q14: [Clinical trial]

How should the cases reported in a double-blind condition in which unblinding reveals that the test drug was not administered be reported?

A. The initial report is submitted only with the blinded test drug and the additional information shows the following:
   - A-1. The only suspected drug is placebo.
   - A-2. In a case from an overseas clinical study, the suspected drug is the comparator not used in clinical studies in Japan (a drug other than study drugs).

B. In studies using multiple study drugs, the initial report is submitted only with the blinded test drug and the additional information shows the following:
   - B-1. The suspected drugs are placebo and study drug(s).

C. The initial report is submitted because the blinded test drug and other study drugs are subject to reporting and the additional information shows the following:

C-1. Unblinding shows that the test drug is placebo or a comparator in cases from overseas clinical studies that has not been used in clinical trials in Japan (a drug other than study drugs), and other study drugs that were considered as suspected drugs remain as drugs subject to reporting.

C-2. Unblinding shows that the test drug is placebo or a comparator in cases from overseas clinical studies that has not been used in clinical trials in Japan (a drug other than study drugs), and other study drugs that were considered as suspected drugs are no longer subject to reporting.

A14: [Clinical trial]

A-1. Since no study drug subject to reporting was administered, the report shall be withdrawn.

A-2. Since no study drug was administered, the report shall be withdrawn. (The suspected comparator was a comparator not used in clinical trials in Japan [a drug other than study drugs], and therefore is not subject to reporting.)

B-1. Since no test drug was administered, but study drugs subject to reporting as suspected drugs remain, an additional report shall be made.

C-1. Since no test drug was administered, but study drugs subject to reporting as suspected drugs remain, an additional report shall be made.

C-2. Since no test drug was administered, but study drugs subject to reporting were administered, an additional report on exclusion from reporting shall be made.

Q15: [Clinical trial]

Although the case still exists, there is no adverse event subject to reporting as a result of the deletion of the adverse event once reported by the investigator after reconsideration, etc. How should this case be reported?

A15: [Clinical trial]

If the event itself does not exist, the report should be withdrawn in the same manner as "when the case itself does not exist." However, this does not apply to the case where there is any adverse event subject to reporting other than the said event (including the case where the causal relationship of the adverse event that was subject to reporting is ruled out or the seriousness, etc. has been changed).

Q16: [Clinical trial]

In the cases in clinical studies conducted overseas, if a causal relationship with the test drug is ruled out and the test drug is not subject to reporting, but study drugs other than the test drug are suspected, are such cases subject to reporting?

A16: [Clinical trials]

The cases for which information has been obtained shall be subject to reporting.

Q17: [Post-marketing] [Clinical trial]

When a clinical trial is switched to and continued as a post-marketing clinical study, is it correct to assume that the marketing authorization holder of each drug, not the post-marketing clinical study sponsor, is responsible for reporting adverse reactions, etc. that occurred during the post-marketing clinical study for drugs used as study drugs during the clinical trial (drugs used in post-marketing clinical studies in the post-marketing clinical study)?

A17: [Post-marketing] [Clinical trial]

It is correct. Note that the sponsor needs to make reports of adverse reactions, etc. in clinical trials if the sponsor learns during the post-marketing clinical study of the adverse reactions, etc. that occurred during the clinical trial before switching.

(2) Reporting deadline, etc.

Q18: [Post-marketing]

In Note 2. (2) in PMSB/SD Notification No. 25 of the Safety Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated March 11, 1998, "Thorough Implementation of Safety Measures for Drugs," it states, "If the information on an event similar to the adverse reaction that is to be newly listed in association with revision of the package insert is obtained before the completion of information transmission to medical institutions, etc. after the revision of the package insert, the event shall be handled as 'an adverse reaction that cannot be expected from PRECAUTIONS' and reported within 15 days." When is the information transmission to medical institutions, etc. considered to be completed?

A18: [Post-marketing]

It shall be the date on which the information transmission determined by the marketing authorization holder is completed.

Q19: [Post-marketing] [Clinical trial]

In post-marketing reports of adverse reactions, etc., when is the reporting deadline when the case was originally considered to be subject to reporting within 30 days, but is found to be subject to reporting within 15 days based on the additional information before the initial report?

In reports of adverse reactions, etc. in clinical trials, when is the reporting deadline when the case was originally considered to be subject to reporting within 15 days, but is found before the initial report to be subject to reporting within 7 days based on the additional information?

A19:

[Post-marketing]

The case shall be reported within 15 days from the date on which it was found to be subject to reporting within 15 days. However, if this reporting deadline comes after 30 days from the date on which information of the case considered to be subject to reporting within 30 days was obtained, at least the information of the case considered to be subject to reporting within 30 days should be reported within 30 days from the date on which the information was obtained.

[Clinical trial]

The case shall be reported within 7 days from the date on which it was found to be subject to reporting within 7 days. However, if this reporting deadline comes after 15 days from the date on which information of the case considered to be subject to reporting within 15 days was obtained, at least the information of the case considered to be subject to reporting within 15 days should be reported within 15 days from the date on which the information was obtained.

Q20: [Clinical trial]

When additional medically important information is obtained and an additional report is to be submitted for an already reported case, is it correct to determine the legal reporting deadline reckoning the date on which additional information was obtained as the base date?

A20: [Clinical trial]

It is correct. An additional report should be submitted within the deadline determined reckoning the date on which additional information was obtained as the base date. For example, if additional information subject to reporting within 7 days is obtained for a case that has already been reported within 15 days, an additional report should be submitted within 7 days. If additional information subject to reporting is obtained for a case that has already been reported within 7 days, an additional report should be submitted within 15 days. In this case, too, the reporting category shall be indicated as 7 days and "Yes" shall be entered for "C.1.7 Does This Case Fulfill the Local Criteria for an Expedited Report?" However, when additional information that should be reported within 7 days (new adverse event, change of adverse event name, change of seriousness or seriousness criteria) is newly obtained, the additional report should be submitted within 7 days.

Q21: [Clinical trial]

How should the reporting deadline be set when the clinical trial in-country representative reports adverse reactions, etc. in clinical trials?

A21: [Clinical trial]

The deadline shall be set using the date (converted to Japan time) on which the sponsor of the clinical trial with no address in Japan or the clinical trial in-country representative (whichever obtained the information first) obtained the information to be reported as the base date for reporting.

(3) Expectedness

Q22: [Post-marketing]

Among the information such as precautions, which items listed in "PRECAUTIONS" can be used for judging whether or not events are expected?

A22: [Post-marketing]

In "PRECAUTIONS" stated based on "Instructions for Electronic Package Inserts of Prescription Drugs" (PSEHB Notification No. 0611-1 dated June 11, 2021), the following items are applicable.

"1. WARNING," "2. CONTRAINDICATIONS," "5. PRECAUTIONS FOR INDICATIONS," "7. PRECAUTIONS FOR DOSAGE AND ADMINISTRATION," "8. IMPORTANT PRECAUTIONS," "9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS," "10. INTERACTIONS," "11. ADVERSE REACTIONS," "12. INFLUENCE ON LABORATORY TESTS," "13. OVERDOSAGE," "14. PRECAUTIONS IN USE"

In "PRECAUTIONS" stated based on "Instructions for Package Inserts of Prescription Drugs" (PAB Notification No. 606 dated April 25, 1997) and "Instructions for Precautions of Prescription Drugs" (PAB Notification No. 607 dated April 25, 1997), the following items are applicable.

"Warning," "Contraindications," "Relative Contraindications," "Precautions for Indications," "Precautions for Dosage and Administration," "Careful Administration," "Important Precautions," "Interactions," "Adverse Reactions," "Use in the Elderly," "Use in Pregnant, Parturient and Nursing Women," "Pediatric Use," "Influence on Laboratory Tests," "Overdosage," "Precautions in Use"

Q23: [Post-marketing]
How do you judge an adverse reaction as unexpected from necessary precautions?

A23: [Post-marketing]
Unexpectedness shall be judged based on “2.4 Unexpected Adverse Reactions” in E2D Guideline, in light of “PRECAUTIONS” among the information such as precautions.

Q24: [Post-marketing]
In the Post-marketing Director-General Notification, it states that “the ‘events not expected from PRECAUTIONS, etc.’ refer to events not mentioned in “PRECAUTIONS” among the information such as precautions (“WARNING,” “Important Precautions,” “Interactions,” “Adverse Reactions,” etc.) or events that are mentioned but are not consistent with the description in nature or severity of symptoms, specificity, etc.” What are examples of the “events that are mentioned in ‘PRECAUTIONS’ but are not consistent with the description in nature or severity of symptoms, specificity, etc.”?

A24: [Post-marketing]
For example, the following cases apply.

(1) When an adverse reaction which is similar in the name to the adverse reaction term listed in “PRECAUTIONS” but different in severity or mechanism of onset occurs (“hepatitis” => “fulminant hepatitis” [“hepatitis” is listed in “PRECAUTIONS” and “fulminant hepatitis” occurs], “anemia” => “aplastic anemia,” “leukopenia, erythropenia, thrombocytopenia” => “pancytopenia,” “leukopenia (granulocytopenia)” => “agranulocytosis,” “diarrhea” => “diarrhea accompanied by dehydration and electrolyte abnormality,” etc.)
(2) When an adverse reaction more specific (limited) than those listed in “PRECAUTIONS” occurs (“acute renal failure” => “interstitial nephritis,” etc.)
(3) When an abnormal test value is mentioned and the abnormal test value occurs with other symptoms (“decreased serum potassium” => “decreased serum potassium accompanied by weakness and arrhythmia,” etc.)

Symptoms and signs that usually occur with the mentioned adverse reactions are expected from “PRECAUTIONS.” (For example, “shock” => “decreased blood pressure, increased heart rate, and decreased urine output associated with shock,” “aplastic anemia” => “pallor and fatigue associated with aplastic anemia,” etc.)

Q25: [Post-marketing]
Can the expectedness of adverse reactions reported overseas be judged based on “PRECAUTIONS" among the information such as precautions in Japan?

A25: [Post-marketing]
It can be judged.

Q26: [Clinical trial]

In the Clinical Trial Director-General Notification, it states, "'Events not expected from the Investigator's Brochure of the test drug concerned or existing scientific findings on the study drugs, etc. other than the test drug concerned' refer to events not stated in the materials used for the latest judgment of expectedness at the time of evaluation of adverse reactions, etc. (the Investigator's Brochure and documents describing scientific findings [the package insert, interview form, academic papers, etc.]; hereinafter referred to as "Investigator's Brochure, etc.") or events that are stated in these materials, but are not consistent with the description in nature, severity of symptoms, or occurrence tendency." What are the "events that are stated in the materials used for the latest judgment of expectedness at the time of evaluation of adverse reactions, etc. but are not consistent with the description in nature, severity of symptoms, or occurrence tendency"?

A26: [Clinical trial]

As shown in PAB/ELD Notification No. 227 of the Evaluation and Licensing Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated March 20, 1995), "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting," events more specific (limited) or more severe than those stated in the Investigator's Brochure, etc. will be regarded as unexpected.

For example, if "acute renal failure" is listed in the Investigator's Brochure, etc. and "Interstitial nephritis" is reported, "interstitial nephritis" will be considered to be unexpected from the Investigator's Brochure, etc.

The same applies to "fulminant hepatitis" as compared to "hepatitis," "aplastic anemia" to "anemia," "pancytopenia" to "leukopenia, erythropenia, thrombocytopenia," "agranulocytosis" to "leukopenia (granulocytopenia)," "diarrhea accompanied by dehydration and electrolyte abnormality" to "diarrhea," etc.

The same applies also when an abnormal test value is mentioned and the abnormal test value occurs with other symptoms (for example, "decreased serum potassium accompanied by weakness and arrhythmia" as compared to "decreased serum potassium").

Symptoms and signs that usually occur with the mentioned adverse reactions are expected from the Investigator's Brochure, etc. (For example, "decreased blood pressure, increased heart rate, and decreased urine output associated with shock" for "shock," "pallor and fatigue associated with aplastic anemia" for "aplastic anemia," etc. are applicable.)

Q27: [Clinical trial]

If an adverse reaction that occurred during a double-blind study has been reported as a "report of adverse reactions, etc. in clinical trials" without unblinding, reflected in the Investigator's Brochure without unblinding, and reported to participating medical institutions, and then the same adverse reaction occurs, is this adverse reaction expected from the Investigator's Brochure or unexpected from the Investigator's Brochure?

A27: [Clinical trial]

After an adverse reaction is reported as a "report of adverse reactions, etc. in clinical trials" without unblinding, reflected in the Investigator's Brochure, and reported to participating medical institutions, it can be handled as expected from the Investigator's Brochure.

Q28: [Clinical trial]

In the case of an adverse reaction reported as unknown, if the event is found to have been caused by a study drug other than the test drug after unblinding of the double-blind study, and no information on adverse reaction reports associated with the test drug concerned has been obtained other than this case, should this adverse reaction be handled as unexpected from the Investigator's

Brochure after unblinding?

A28: [Clinical trial]

The interpretation is correct.

Q29: [Clinical trial]

When making an additional report after unblinding of a double-blind study revealed administration of placebo and another study drug is a suspected drug, is it acceptable to either enter the information on placebo or not enter it after deleting the information on the test drug that was included in the previous report in the data elements under "Drug Identification (G.k.2)"?

A29: [Clinical trial]

It is acceptable.

Q30: [Clinical trial]

Regarding the attachment of E2B (R3) Two Director Notification, 8. (1) D. and F., if the sponsor and the marketing authorization holder applying for approval are different and the sponsor cannot obtain the summary of the product application, is it acceptable to use the Investigator's Brochure as the basis for the judgment of expectedness for reports of adverse reactions, etc. from the sponsor?

A30: [Clinical trial]

It is acceptable.

Q31: [Clinical trial]

In reports of adverse reactions, etc. to study drugs other than the test drug, can the sponsor select the "documents describing scientific findings" for each study drug?

A31: [Clinical trial]

The sponsor can select it.

Q32: [Clinical trial]

In the attachment of E2B (R3) Two Director Notification, 8. (1) B., it states, "an adverse reaction shall be judged as being 'expected' on the day of preparation or revision of the latest Investigator's Brochure or the documents describing the latest scientific findings." How can the date of revision be defined when using the package inserts or interview forms of other companies' products as the documents describing the latest scientific findings on study drugs other than the test drug?

A32: [Clinical trial]

When using the package inserts or interview forms of other companies' products as the documents describing the latest scientific findings on study drugs other than the test drug, it is acceptable to consider the date on which revision information is obtained as the date of revision, but efforts should be made to obtain the revision information promptly.

(4) Criteria for determination of seriousness

Q33: [Post-marketing]

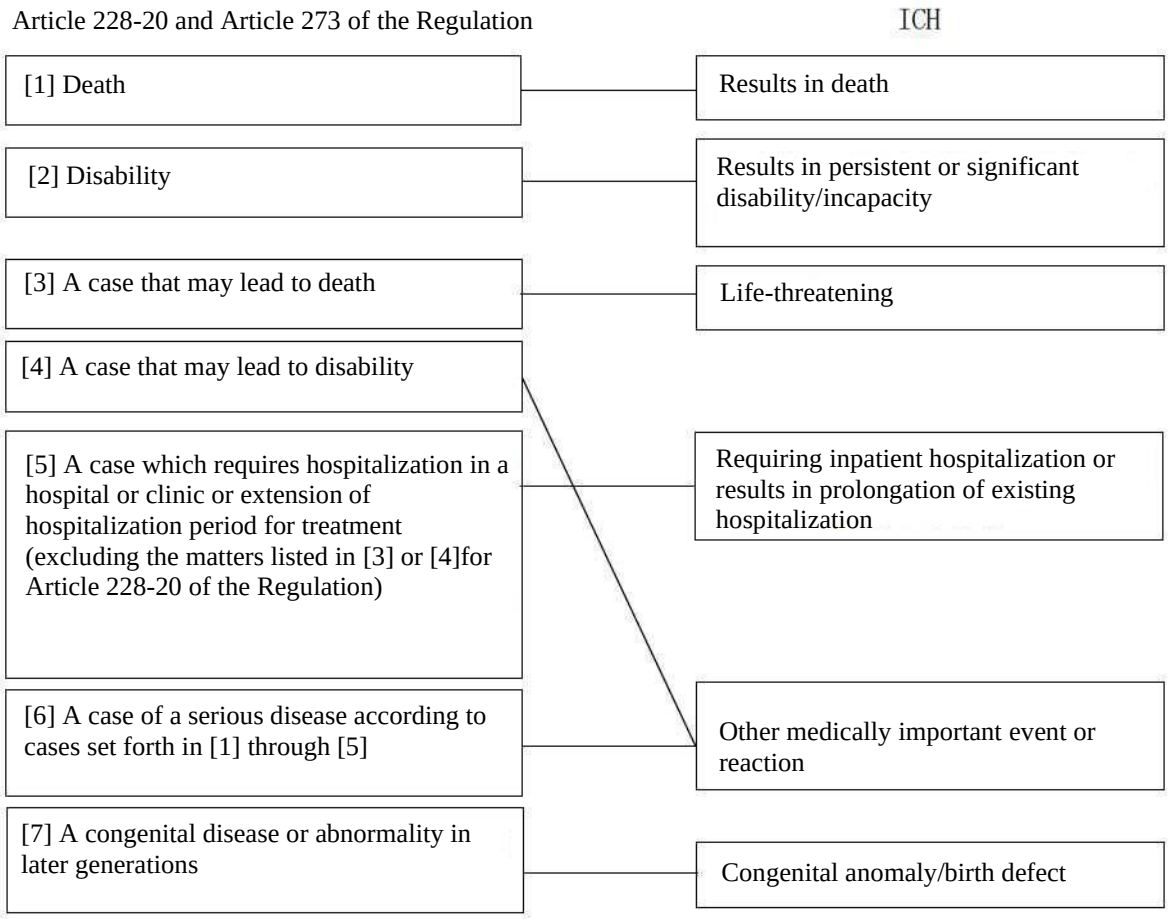
What actions should be taken if information on occurrence of an adverse reaction has been obtained, but there is no information to be used for evaluation of seriousness?

A33: [Post-marketing]

Efforts should be made to collect detailed information so that the seriousness can be evaluated, and the seriousness should be evaluated for each adverse reaction that occurred based on the obtained information.

Q34: [Post-marketing] [Clinical trial]
How should the association with the definition of seriousness of adverse reactions by ICH be considered?

A34: [Post-marketing] [Clinical trial]
Refer to the table below.



Q35: [Post-marketing]
How should “death” in Article 228-20 of the Regulation be interpreted?

A35: [Post-marketing]
It refers to deaths suspected to have been caused by adverse reactions, which falls under the ICH definition (see E2D Guideline) of “Results in death.” For example, in the case where a patient developed an infection due to granulocytopenia, bone marrow depression, etc. and died, this case naturally falls under the category of fatal cases subject to reporting of adverse reactions, etc. Even if the reporter has not determined that the cause of death is an adverse reaction, the case shall be handled as a case of death caused by an adverse reaction if the sender has judged that the death was caused by an adverse reaction.

Q36: [Post-marketing]
How should “disability” in Article 228-20 of the Regulation be interpreted?

A36: [Post-marketing]
It refers to the onset of incapacity that interferes with daily life and corresponds to “Results in persistent or significant disability/incapacity” in the ICH provisions (see E2D Guideline).

Q37: [Post-marketing]
How should “A case that may lead to death” in Article 228-20 of the Regulation be interpreted?

A37: [Post-marketing]
It corresponds to “Life-threatening” in the ICH provisions (see E2D Guideline) and refers to the case where the patient was at risk of death at the time of the occurrence of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Q38:[Post-marketing]
How should “A case that may lead to disability” in Article 228-20 of the Regulation be interpreted?

A38: [Post-marketing]
It refers to the case where the patient was at risk of developing incapacity that interferes with daily life when the adverse reaction occurred. It corresponds to “Other medically important event or reaction” in the ICH provisions (see E2D Guideline). It does not refer to an event that hypothetically might have caused disability if it were more severe.

Q39: [Post-marketing]
How should “A case which requires hospitalization in a hospital or clinic or extension of hospitalization period for treatment” in Article 228-20 of Regulation be interpreted?

A39: [Post-marketing]
It corresponds to “Requiring inpatient hospitalization or prolongation of existing hospitalization” in the ICH provisions (see E2D Guideline). It refers to cases of hospitalization or prolonged hospitalization for the treatment of adverse reactions, even if the patient has been hospitalized for the treatment of adverse reactions but receives no particular treatment (bed rest as treatment). For example, cases of hospitalization due to anaphylactic shock or pseudomembranous colitis fall under this category. Hospitalization or prolongation of hospitalization for tests or hospitalization for follow-up observation after the adverse reaction is cured or improved are not included.

Q40: [Post-marketing]
How should “A case of death or a serious disease according to cases set forth in (1) through (3)” in Article 228-20, Paragraph 1, Item 1, C (4) of the Regulation be interpreted?

A40: [Post-marketing]

It corresponds to "Other medically important event or reaction" in the ICH provisions (see E2D Guideline), that is, important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention or treatment to prevent one of other outcomes such as "results in death," "results in persistent or significant disability/incapacity," "life-threatening," and "requiring inpatient hospitalization or prolongation of existing hospitalization." Examples are allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Q41: [Post-marketing]

How should "A congenital disease or abnormality in later generations" in Article 228-20 of the Regulation be interpreted?

A41: [Post-marketing]

It corresponds to "Congenital anomaly/birth defect" in the ICH provisions (see E2D Guideline) and to the case where exposure to a drug before or during pregnancy is suspected to have caused abnormality in an infant. Examples include hypoplasia caused by thalidomide and vaginal cancer in a female infant caused by diethylstilbestrol.

(5) Description guideline

Q42: [Post-marketing]

Regarding the items that can be briefly written in Appendices 1 and 2 of the E2B (R3) Two Director Notification, how should these items be written?

A42: [Post-marketing]

Since these items, except E.i.1.1a, E.i.1.1b, and E.i.1.2, definitely need to be written when a completion report is submitted, and if they are not written at all, the report will be an error. Therefore, they shall be written in simplified expressions with reference to the "Supplement" column of "Value allowed-related" in the tables in Appendices 1 and 2.

Q43: [Post-marketing] [Clinical trial]

Are there any precautions for writing the time zone?

A43: [Post-marketing] [Clinical trial]

See Appendix II of the E2B (R3) Implementation Guide for how to write dates/times. Inter-item data check, etc. will be performed considering the time without time zone as Japan time (+ 09:00) and converting the time with time zone to Japan time. Handle the time zone carefully.

Q44: [Post-marketing] [Clinical trial]
Is the use of full-width characters acceptable for the input types, "NUM" and "date (minimum precision)"?

A44: [Post-marketing] [Clinical trial]
Enter the input types, "NUM" and "date (minimum precision)," with half-width characters.

Q45: [Post-marketing] [Clinical trial]
Is the use of characters with an umlaut mark acceptable for the input type, "TXT"?

A45: [Post-marketing] [Clinical trial]
Characters with an umlaut mark, etc. can be accepted as long as they are available in UTF-8. However, it is desirable not to use characters with an umlaut mark to state cases in Japan. Letter types such as "<" or ">" that are not permitted in the XML messages cannot be used.

(6) J data elements

Q46: [Post-marketing] [Clinical trial]
Which base date for reporting should be entered in "J2.2.1 Base date for reporting" when, in a post-marketing report of adverse reactions, etc., the event was originally considered to be subject to reporting within 30 days, but was found to be subject to reporting within 15 days based on the additional information before the initial report, and the contents of reporting within 30 days and those of reporting within 15 days are to be reported together? Should 15-day reporting be specified in "C.1.7 Does This Case Fulfill the Local Criteria for an Expedited Report?"?
Which base date for reporting should be entered in "J2.2.1 Base date for reporting" when, in a report of adverse reactions, etc. in clinical trials, the event was originally considered to be subject to reporting within 15 days, but was found to be subject to reporting within 7 days based on the additional information before the initial report, and the contents of reporting within 15 days and those of reporting within 7 days are to be reported together? Should 7-day reporting be specified in "C.1.7 Does This Case Fulfill the Local Criteria for an Expedited Report?"?

A46:

[Post-marketing]
The "J2.2.1 Based date of reporting" shall be the date on which the information that the event is subject to reporting within 30 days was obtained. Explain the relationship among the base date for reporting, date on which additional information was obtained, and reporting deadline in "J2.2.2 Comment on Base Date for Reporting." Specify 15-day reporting in "C.1.7 Does This Case Fulfill the Local Criteria for an Expedited Report?"

[Clinical trial]
The "J2.2.1 Based date of reporting" shall be the date on which the information that the event is subject to reporting within 15 days was obtained. Explain the relationship among the base date for reporting, date on which additional information was obtained, and reporting deadline in "J2.2.2 Comment on Base Date for Reporting." Specify 7-day reporting in "C.1.7 Does This Case Fulfill the Local Criteria for an Expedited Report?"

Q47: [Post-marketing]

For a drug with a new active ingredient to be studied during the re-examination period in an early post-marketing phase vigilance newly required because of addition of indications, etc., when an adverse reaction occurs after completion of the early post-marketing phase vigilance in association with the use for the indication, etc. subject to the early post-marketing phase vigilance, which status category should be selected for "J2.4.k Status Category of New Drugs, etc."?

A47: [Post-marketing]

If the onset of the case is within 2 years after the approval of the additional indication, etc., it should be reported as "within 2 years after approval," and if it is more than 2 years after the approval of the additional indication, etc., it should be reported as "Not applicable." However, when the approval of the additional Indication, etc. is obtained after the expiration of the re-examination period, the case should be reported as "Not applicable" even if it occurs within 2 years after the approval.

Q48: [Post-marketing] [Clinical trial]

Why are symbols indicating repetition in J data elements such as "k" and "i" are used differently as in "J2.4.k Status Category of New Drugs, etc." and "J2.14.i Unknown/known"?

A48: [Post-marketing] [Clinical trial]

The repetition symbols in the J data elements correspond to the repetition symbols for the E2B (R3) data elements as follows. In the management system for information on adverse drug reactions, XPath is used to acquire values. "J2.4.k" belonging to "G.k" first acquired by XPath corresponds to the first repetition.

<table>
<tr><td colspan="2">J data elements</td><td colspan="2">E2B (R3) data elements</td></tr>
<tr><td>J2.4.k</td><td>Status Category of New Drugs, etc.</td><td rowspan="3">G.k</td><td rowspan="3">Drug(s) Information</td></tr>
<tr><td>J2.5.k</td><td>Risk Category, etc. of Over-the-counter Drugs, etc.</td></tr>
<tr><td>J2.6.k</td><td>Route of Obtaining Over-the-counter Drugs</td></tr>
<tr><td>J2.14.i</td><td>Unknown / Known</td><td>E.i</td><td>Reaction(s) / Event(s)</td></tr>
<tr><td>J2.15.r</td><td>Country of Publication</td><td rowspan="2">C.4.r.1</td><td rowspan="2">"Publication Status" of Research / Action Reports</td></tr>
<tr><td>J2.17.r</td><td>Study / Research Classification</td></tr>
</table>

Q49: [Clinical trial]

For study drugs such as the following, what should be selected for "J2.4.k Status Category of New Drugs, etc."?

[1] When a drug which is manufactured and marketed in foreign countries and has the same ingredients as drugs approved in Japan (foreign pharmaceutical) is used as a test drug

[2] When a drug which is manufactured and marketed in foreign countries and has the same ingredients as drugs approved in Japan (foreign pharmaceutical) is used as a study drug (excluding test drugs)

A49: [Clinical trial]

[1] Select "4 = clinical trial for partial change ongoing."

[2] Select "8 = approved in Japan (excluding the test drug)."

According to the approval status of active ingredients in Japan, an appropriate selection should be made from "3 = unapproved" and "4 = clinical trial for partial change ongoing" in the case of a test drug, and from "8 = approved in Japan (excluding the test drug)" and "9 = not approved in Japan (excluding the test drug)" in the case of a study drug other than the test drug.

Q50: [Clinical trial]
Information on study drugs is to be entered in "Presence or Absence of Cases Being Treated (J2.13.r.4)." What information should be entered in "Presence or Absence of Cases Being Treated (J2.13.r.4)"?

A50: [Clinical trial]
With or without the administration in the report concerned, enter the status of all study drugs stated in the clinical trial notification or notification of changes in clinical trial plan for the main test drug. In this case, it is acceptable to enter information assuming only the study drugs used in the study of the main test drug.

Q51: [Clinical trial]
In a clinical trial using multiple test drugs, if the main test drug has been approved or its development has been discontinued, but no new notification on changes in the main test drug is made, how should adverse reactions, etc. be reported?

A51: [Clinical trial]
Even if the main test drug is approved or its development is discontinued, the information on the main test drug which is approved or development of which is discontinued shall be written in "Test Substance Identification Code (J2.12)" and "Outline of Clinical Trial in Japan (J2.13)."
For the main test drug which has been approved or the development of which has been discontinued, reports of adverse reactions, etc. in clinical trials are not required.

Q52: [Clinical trial]
Should the latest version of the code system of J data elements be used for reporting even during the period of the transitional measures?

A52: [Clinical trial]
It is desirable to use the latest version of the code system, but the available versions should be checked on the PMDA's "website for drug marketing authorization holders" (SKW site).

(7) ICSR data elements

Q53: [Post-marketing] [Clinical trial]
In "N.1.5 Date of Batch Transmission," "N.2.r.4 Date of Message Creation," and "C.1.2 Date of Creation," year, month, day, hour, minute, and second are to be entered. What should be done if there is a time lag between the time of creation of a file such as ICSR and the time of transmission of the data?

A53: [Post-marketing] [Clinical trial]

When preparing ICSR files, etc., “N.2.r.4” and “C.1.2” shall completely match. For “N.1.5,” enter the date (year, month, day, hour, minute, and second), considering the time shall be set after the preparation time in “N.2.r.4,” etc. In the additional reports, an error occurs if the date in “C.1.2” is the same as the date in the previous report. Make sure to enter the date, considering that the time shall be set after the previous report.

For submissions of CD, etc., “0000” may be entered for a minute and a second.

Q54: [Clinical trial]

When two companies jointly developing the drug submit a report on adverse reactions, etc., respectively, is it acceptable for the sponsor that made the report of adverse reactions, etc. earlier to notify the other sponsor of “C.1.1 Sender’s (Case) Safety Report Unique Identifier”?

A54: [Clinical trial]

It is desirable for the sponsor that made the report on adverse reactions, etc. first to notify the co-development company of “C.1.1,” “C.1.8.1 Worldwide Unique Case Identification Number,” etc. using the ICSR file. At the time of preparation of the ICSR file, the sponsor that received the notification shall enter the provided “C.1.8.1” in “C.1.8.1,” enter “true” (= Yes) in “C.1.9.1 Other Case Identifiers in Previous Transmissions,” enter the name of the other organization in “C.1.9.1.r.1 Source(s) of the Case Identifier,” and enter the provided “C.1.1” in “C.1.9.1.r.2 Case Identifier(s).”

Q55: [Post-marketing] [Clinical trial]

When reporting by postal mail, is it correct to enter the date of mailing in “N.1.5 Date of Batch Transmission,” “N.2.r.4 Date of Message Creation,” and “C.1.2 Date of Creation”?

A55: [Post-marketing] [Clinical trial]

It is correct. When submitting a CD, etc., “0000” may be entered for a minute and a second.

Q56: [Post-marketing]

For a report on an in-house marketed drug based on the data obtained from a clinical trial conducted by another company, is it correct to select “2 = Report from study” for “C.1.3 Type of report”?

A56: [Post-marketing]

It is correct.

Q57: [Post-marketing] [Clinical trial]

When a reporter has suspected the possibility of infection caused by the use of a drug or a study drug and has told a medical representative, etc. about it, but the reporter concerned wishes to make a final judgment by looking at the result of another test (virus marker), is it correct to enter the date of the reporter's final judgment based on the result of another test in “C.1.4 Date Report was First Received from Source”?

A57: [Post-marketing] [Clinical trial]

The date should be the date on which the reporter informed the medical representative, etc. of the possibility of infection caused by the use of the drug or the study drug.

Q58: [Post-marketing]
When a marketing authorization holder is outsourcing a part of post-marketing safety management operations, is it correct to enter the date on which the marketing authorization holder has received the information from the contractor in “C.1.4 Date Report Was First Received from Source”?

A58: [Post-marketing]
Handle the date on which either the marketing authorization holder or the contractor first obtained the information as “C.1.4.”

Q59: [Clinical trial]
When the clinical trial in-country representative reports adverse reactions, etc. regarding study drugs, when should “C.1.4 Date Report Was First Received from Source” be?

A59: [Clinical trial]
The date should be the time when either the sponsor of the clinical trial with no address in Japan (hereinafter referred to as “overseas sponsor”) or the clinical trial in-country representative first obtained the information concerned.

Q60: [Post-marketing] [Clinical trial]
When a case identical to a case reported in a “report of adverse reactions, etc. in clinical trials” is reported as a “post-marketing report of adverse reactions, etc.,” is it always necessary to provide the identifier in each report in “C.1.8.1 Worldwide Unique Case Identification Number” and "C.1.10.r Identification Number of the Report Which Is Linked to This Report"?

A60: [Post-marketing] [Clinical trial]
The same identifier should be provided in the “post-marketing report of adverse reactions, etc.” and the “report of adverse reactions, etc. in clinical trials” for “C.1.8.1,” and the identifier in each report should be entered in “C.1.10.r” where possible. In addition, in “J2.11 Other Reference Matters, etc.,” it shall be stated that the “report of adverse reactions, etc. in clinical trials” (or the “post-marketing report of adverse reactions, etc.”) has already been submitted or is scheduled to be submitted, and if it has already been submitted, “J2.1 Identification Number” of the report concerned shall also be entered.

Q61: [Post-marketing] [Clinical trial]
When a case identical to a case reported in a “report of adverse reactions, etc. in clinical trials" is reported as a “post-marketing report of adverse reactions, etc.," should the same value be used for the company's unique case report number, etc. (“C.1.1 Sender’s (Case) Safety Report Unique Identifier” and “N.2.r.1 Message Identifier”) when reporting as a “report of adverse reactions, etc. in clinical trials” and when reporting as a “post-marketing report of adverse reactions, etc.”? Or, should different values be used?

A61: [Post-marketing] [Clinical trial]
Different values should be used.

Q62: [Post-marketing] [Clinical trial]
If the patient’s abbreviated name is partially unknown or not entered, or not entered at all, is it acceptable to enter “X.X.” in “D.1 Patient (name or initials)”?

A62: [Post-marketing] [Clinical trial]

If the patient's abbreviated name is unknown, not entered, etc., it should be entered as NullFlavor in “D.1 Patient (name or initials).” If the patient's abbreviated name is known but not entered to protect personal information, NullFlavor = MSK shall be used.

See Attachment 1 and 2 of the E2B (R3) Implementation Guide and E2B (R3) ICH Q&A for the use of NullFlavor.

Q63: [Post-marketing] [Clinical trial]
Is it necessary to list all adverse reactions/infections reported by the reporter in “E.i Reaction(s) / Event(s) (repeat as necessary)”?

A63: [Post-marketing] [Clinical trial]

All adverse reactions/infections reported by reporters may be stated, but it is also acceptable to list only the names of adverse reactions/infections subject to reporting based on the provisions of Article 228-20 and Article 273 of the Regulation.

Q64: [Post-marketing] [Clinical trial]
When entering the names of adverse reactions, is it acceptable to enter, for example, only “shock” for “decreased blood pressure, increased heart rate, decreased urinary output, etc.” associated with “shock”?

A64: [Post-marketing] [Clinical trial]

It is acceptable to list only “shock” in “E.i Reaction(s) / Event(s) (repeat as necessary)” when the reporter determines that the case is a case of “shock.” However, the associated symptoms, “decreased blood pressure, increased heart rate, decreased urinary output, etc.” should be entered in “H.1 Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information.”

For details of the description, see “MedDRA TERM SELECTION: POINTS TO CONSIDER” (PTC).

Q65: [Post-marketing] [Clinical trial]
Is it correct not to enter information in “E.i.1.2 Reaction / Event as Reported by the Primary Source for Translation” if “E.i.1.1a Reaction / Event as Reported by the Primary Source in Native Language” is written in Japanese or English?

A65: [Post-marketing] [Clinical trial]

It is correct. If “E.i.1.1a” is written in a language other than Japanese or English, it should be written in “E.i.1.2” in Japanese or English.

Q66: [Post-marketing] [Clinical trial]
If the reporter is not a healthcare professional (e.g. consumer or other non-healthcare professional), should “E.i.3.1 Term Highlighted by the Reporter” be interpreted as “not highlighted by the reporter” or left blank as “unknown”?

A66: [Post-marketing] [Clinical trial]

Regardless of the reporter's qualification, it should be written as determined by the reporter.

Q67: [Post-marketing] [Clinical trial]
How should the outcome of adverse reactions that did not cause death be stated in "E.i.7 Outcome of Reaction / Event at the Time of Last Observation"?

A67: [Post-marketing] [Clinical trial]
An appropriate outcome other than "death" should be selected for each adverse reaction.

Q68: [Post-marketing] [Clinical trial]
In "E.i.7 Outcome of Reaction / Event at the Time of Last Observation," which should be entered, outcome of the mother or the outcome of the fetus, if the mother has had miscarriage?

A68: [Post-marketing] [Clinical trial]
In the case of fetal death or early spontaneous abortion, the outcome of the parent for the adverse reaction term (fetal death, etc.) should be entered. For example, "1 = Recovered/resolved" can be selected if the parent has recovered.

Q69: [Post-marketing] [Clinical trial]
Is it acceptable to think that the description in "E.i.8 Medical Confirmation by Healthcare Professional" is not necessary if "C.2.r.4 Qualification" is "1 = Physician," "2 = Pharmacist," or "3 = Other healthcare professional"?

A69: [Post-marketing] [Clinical trial]
It is acceptable. If C.2.r.4 is "4 = Lawyer" or "5 = Consumer or other non-health professional," state whether or not medical confirmation is provided in E.i.8.

Q70: [Post-marketing] [Clinical trial]
When stating the result of drug lymphocyte stimulation test (DLST), the MedDRA LLT code for DLST can be entered in "F.r.2.2b Test Name (MedDRA code)." In which elements should the name of the drugs used in DLST be provided?

A70: [Post-marketing] [Clinical trial]
Enter the MedDRA LLT code for DLST in "F.r.2.2b Test Name (MedDRA code)" and the names of the drugs and the result of the test in "F.r.3.4 Result Unstructured Data."

Q71: [Post-marketing] [Clinical trial]
Is it necessary to list other companies' suspected drugs in "G.k.4.r.7 Batch / Lot Number"?

A71:

[Post-marketing]
If a suspected drug of another company is a vaccine, try to obtain the information of the batch/lot number and enter it as much as possible.

[Clinical trial]
If a suspected drug that falls under the category of other drugs is a vaccine, try to obtain the information of the batch/lot number and enter it as much as possible.

Q72: [Post-marketing]

There are cases where “G.k.2.1 Medicinal Product Unique Identifier / Pharmaceutical Product Unique Identifier,” etc. cannot be identified because "G.k.4.r Dosage and relevant information (repeat as necessary)" or "G.k.7.r Indication for use in case," etc. is unknown. If the sender has obtained the approval of multiple drug products (different brand names), specifications (different strengths), dosage forms (different dosage forms with the same route of administration) or routes of administration for the same active ingredient, which drug should be reported?

A72: [Post-marketing]

Investigate and try to identify the drug. Even if the drug cannot be identified as a result, the drug considered relatively more appropriate should be reported based on the obtained information. If it is impossible to judge which drug is relatively more appropriate, it is acceptable to report the most commonly used drug.

Q73: [Post-marketing]

How should “G.k.4.r.2 Number of Units in the Interval” and “G.k.4.r.3 Definition of the Time Interval Unit” be written when the dosing interval of the drug is three times a day?

A73: [Post-marketing]

In the case of three times daily, enter “8” in “G.k.4.r.2” and a UCUM code indicating “time” in “G.k.4.r.3.” Similarly, in the case of twice daily, enter “12” and a UCUM code indicating “time,” respectively; in the case of every other day, enter “2” and a UCUM code indicating “day,” respectively; in the case of once weekly, enter “1” and a UCUM code indicating “week,” respectively.

Q74: [Post-marketing] [Clinical trial]

If an adverse reaction, etc. occurred during the treatment with a suspected drug, but the treatment was continued and the adverse reaction, etc. concerned resolved during the treatment period, how should “G.k.9.i.3.2 Time Interval between Last Dose of Drug and Start of Reaction / Event” be written?

A74: [Post-marketing] [Clinical trial]

Leave “G.k.9.i.3.2” blank and enter information in “H.1 Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information.”

Q75: [Post-marketing] [Clinical trial]

What should be done for drugs with characters such as “輸,” “東薬,” “愛薬,” “阪,” etc. in the approval numbers?

A75: [Post-marketing] [Clinical trial]

Read the approval numbers according to “Handling, etc. of Flexible Disk Applications, etc.” (PSEHB/PED Notification No. 0216-1, PSEHB/MDED Notification No. 0216-1 issued jointly by the Director of Pharmaceutical Evaluation Division and the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated February 16, 2022).

Q76: [Clinical trial]

For “Reports of infection cases in Japan (clinical trials)” and “Reports of adverse reaction cases in Japan (clinical trials),” is it correct to enter the test substance identification code in “G.k.2.2 Medicinal Product Name as Reported by the Primary Source” if a test drug with the same active ingredient as that of approved drugs and different dosage form and route of administration is currently being developed?

A76: [Clinical trial]

Enter the test substance identification code.

Q77: [Clinical trial]

In the case of study drugs not approved in Japan excluding test drugs, the overseas brand names are to be entered in half-width alphanumeric characters. What should be entered if the brand names do not exist or are unknown?

A77: [Clinical trial]

Enter the information such as generic names in half-width alphanumeric characters.

Q78: [Clinical trial]

What should be entered in “G.k.2.2 Medicinal Product Name as Reported by the Primary Source” for suspected drugs other than study drugs?

A78: [Clinical trial]

Enter the 9-digit or 7-digit (for prescription drugs) or 12-digit (for drugs requiring guidance or over-the-counter drugs) codes whenever possible. For drugs with no or unclear 9-digit re-examination code, but with a 7-digit re-examination code, enter the 7-digit re-examination code in “G.k.2.3.r.1 Substance / Specified Substance Name” and be sure to enter it in “G.k.2.2 Medicinal Product Name as Reported by the Primary Source” as well. Enter the brand name if the code is unknown. If neither is known, available information such as generic name shall be provided in Japanese or English.

Q79: [Clinical trial]

What should be entered in "G.k.2.3.r.1 Substance / Specified Substance Name” for the study drug that falls under the category of foreign pharmaceuticals other than suspected drugs?

A79: [Clinical trial]

Enter the 7-digit (for prescription drugs) or 12-digit (for drugs requiring guidance or over-the-counter drugs) codes whenever possible. If the code is unknown, enter the generic name (brand name for drugs requiring guidance or over-the-counter drugs). If neither code nor generic name is known, available information shall be provided in Japanese or English.

Q80: [Clinical trial]

What should be entered in "G.k.2.3.r.1 Substance / Specified Substance Name” for the suspected drugs other than study drugs if generic names are identified?

A80: [Clinical trial]

Enter 7-digit (for prescription drugs) or 12-digit (for drugs requiring guidance or over-the-counter drugs) codes whenever possible. If the code is unknown, enter the generic name (brand name for drugs requiring guidance or over-the-counter drugs). If neither code nor generic name is known, available information shall be provided in Japanese or English.

Q81: [Clinical trial]

Different test substance identification codes are used depending on the route of administration for the drugs with the same active ingredient and different routes of administration. A clinical trial notification has been submitted using each test substance identification code as the main test drug.

If any overseas adverse reaction case is obtained for the active ingredient concerned, how can it be reported?

A81: [Clinical trial]

Report by either one of the following methods.

(1) Report for each investigational ingredient code of the main test drug.

(2) Make one report by stating the items related to the drug name referring to the following example.

<Example>

If the test substance identification codes of two drugs are ChikenA-Tab and ChikenA-INJ, respectively, take actions according to the following situations from [1] to [3] depending on the status of determination of the generic name, etc. of the active ingredient.

The test substance identification code written in "J2.12 (Test Substance Identification Code)" may be either "ChikenA-Tab" or "ChikenA-INJ."

[1] When the active ingredient has not been approved in Japan and no generic name has been determined

J2.12 (Test Substance Identification Code): "ChikenA-Tab"

G.k.2.2 (Medicinal Product Name as Reported by the Primary Source): "$ChikenA-Tab$$ChikenA-INJ$" (Each investigational ingredient code should be sandwiched by the symbol, $, and all investigational ingredient codes subject to reporting should be listed.)

G.k.2.3.r.1 (Substance / Specified Substance Name): Enter ChikenA (arbitrary name indicating the active ingredient concerned) or "generic name undetermined." The investigational ingredient code notified in the clinical trial notification shall not be used as an arbitrary ingredient name.

[2] When the active ingredient has not been approved in Japan and its generic name has been determined (e.g., JAN: "Chikenmab")

J2.12 (Test Substance Identification Code): "ChikenA-Tab"

G.k.2.2 (Medicinal Product Name as Reported by the Primary Source): "$ChikenA-Tab$$ChikenA-INJ$" (Each test substance identification code should be sandwiched by the symbol, $, and all test substance identification codes subject to reporting should be listed.)

G.k.2.3.r.1 (Substance / Specified Substance Name): "Chikenmab"

[3] When the active ingredient has been approved in Japan (e.g., JAN: "Chikenmab" and the re-examination code: "1234567" [7-digit re-examination code], "123456789" [9-digit re-examination code])

(Response 1)

J2.12 (Test Substance Identification Code): "ChikenA-Tab"

G.k.2.2 (Medicinal Product Name as Reported by the Primary Source): "$ChikenA-Tab$$ChikenA-INJ$" (Each test substance identification code should be sandwiched by the symbol, $, and all test substance identification codes subject to reporting should be listed.)

G.k.2.3.r.1 (Substance / Specified Substance Name): "Chikenmab"

(Response 2)
J2.12 (Test Substance Identification Code): “ChikenA-Tab”
G.k.2.2 (Medicinal Product Name as Reported by the Primary Source): “123456789”
G.k.2.3.r.1 (Substance / Specified Substance Name): “1234567”

When using the method in Response 2, an application form stating that a report of overseas adverse reactions in clinical trials with “123456789” in “G.k.2.2” is about the test substance identification codes, “ChikenA-Tab” and “ChikenA-INJ,” shall be submitted beforehand. When this application form is submitted, its contents should be confirmed in advance with Review Planning Division, Office of Review Management, PMDA.

For drugs such as generic drugs for which a 9-digit re-examination code is not assigned, but a 7-digit re-examination code is known, enter the 7-digit re-examination code (e.g., “1234567”) in “G.k.2.2 (Medicinal Product Name as Reported by the Primary Source).”

Q82: [Post-marketing]
As the “brand name” for overseas cases, which should be provided in “G.k.2.2 Medicinal Product Name as Reported by the Primary Source,” the brand name in the country where the adverse reaction occurred or the brand name in Japan?

A82: [Post-marketing]
Enter the overseas brand name in half-width alphanumeric characters for drugs other than in-house suspected drugs.

In the case of an in-house suspected drug, enter the code of the drug product which the sender considers to be relatively more appropriate among those for which the sender has obtained the marketing approval in Japan in light of the reason for use of the drug in the case, dosage and administration, other active ingredients contained, etc.

Q83: [Post-marketing] [Clinical trial]
If there are multiple reporters and the “C.2.r.4 Qualification” includes both “1 = Physician,” “2 = Pharmacist,” or “3 = Other health professional” and “4 = Lawyer” or “5 = Consumer or other non-health professional,” should the evaluation of causal relationship by “4 = Lawyer” or “5 = Consumer or other non-health professional” be entered in “G.k.9.i.2.r Assessment of Relatedness of Drug to Reaction(s) / Event(s) (repeat as necessary)”?

A83: [Post-marketing] [Clinical trial]
If the reporters include “1 = Physician,” “2 = Pharmacist,” or “3 = Other health professional,” the evaluation of causal relationship by “4 = Lawyer” or “5 = Consumer or other non-health professional” does not have to be entered in “G.k.9.i.2.r.”

Q84: [Post-marketing] [Clinical trial]
When a clinical trial is conducted for the purpose of partial changes in approved product information related to addition, change, or deletion of dosage and administration or indications of drugs already approved for marketing in Japan, the party that has obtained the approval is to enter “TIKEN” in half-width alphabet characters in the column of “G.k.11 Additional Information on Drug,” etc. when making reports of overseas infection cases or reports of overseas adverse reaction cases based on the provisions of Article 228-20 of the Regulation. What should be entered if there are multiple suspected drugs other than the test drug of the clinical trial concerned?

A84: [Post-marketing] [Clinical trial]

Enter “TIKEN” in half-width alphabet characters only for the test drug of the clinical trial.

Q85: [Post-marketing] [Clinical trial]

In the case of fetal death or early spontaneous abortion, where should the gestation period at the time of fetal death or early spontaneous abortion be entered, in “D.2.2.1 Gestation Period When Reaction / Event Was Observed in the Foetus” or “H.1 Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information”?

A85: [Post-marketing] [Clinical trial]

In the case of fetal death or early spontaneous abortion, the patient is the mother and therefore the gestation period shall be entered not in “D.2.2.1,” but in “H.1.” Enter information in “D.2.2.1” if an adverse reaction occurs in the fetus and the fetus is considered to be the patient.

Q86: [Post-marketing] [Clinical trial]

For an overseas case, if the opinion of the foreign company has already been entered in English in “H.4 Sender's Comments,” can the report be submitted in English?

A86: [Post-marketing] [Clinical trial]

It can be submitted in English. If the opinion of a foreign company is written in a language other than English or Japanese, it should be translated into English or Japanese. The sender’s opinion should be entered in Japanese, separately from the opinion of the foreign company.

Q87: [Clinical trial]

“H.4 Sender’s Comments” is a required element, but is it necessary to enter the comments even if the clinical trial in-country representative is the sender?

A87: [Clinical trial]

It is not necessary. However, state the opinion of the overseas sponsor in “H.4.”

Q88: [Post-marketing] [Clinical trial]

The E2B (R3) Implementation Guide states that “if there are multiple information sources, the person who initially reported the fact to the sender concerned shall be the ‘primary source for regulatory purposes.’” For cases received via authorities or affiliate companies, who is the primary source of information?

A88: [Post-marketing] [Clinical trial]

Even if a report of adverse drug reactions, etc. is forwarded, the primary source of information for the report will not change. Therefore, the person who was used as the primary source of information by regulatory authorities or partner companies, etc. which mediated the information should be the primary source of information.

Q89: [Post-marketing] [Clinical trial]

If the report of adverse reactions, etc. includes a CIOMS report form or a MedWatch report form related to the case report of adverse drug reactions, etc. concerned, is it acceptable not to state it in "C.1.6.1.r.1 Documents Held by Sender"?

A89:

[Post-marketing]

It is acceptable not to state it. However, for reports of overseas infection cases (post-marketing) and reports of overseas adverse reaction cases (post-marketing), if the entry is simplified for reporting by attaching the materials stating the case information such as the CIOMS report form to the ICSR file, the names of the materials corresponding to this element shall be entered and the materials shall be attached to "C.1.6.1.r.2 Included documents" (C.4.r.1/C.4.r.2 for literature). In this case, it is acceptable not to enter the elements other than essential ones and those required to be entered because of the contents of other elements. Note that only materials in English or Japanese or those translated into English or Japanese can be attached, and no hand-written materials can be attached in this case.

[Clinical trial]

It is acceptable not to state it.

Q90: [Post-marketing]

When an in-house drug is reported using a provisional code, an additional report is to be made promptly when a re-examination code is given. Is it necessary to make an additional report only because a re-examination code is given?

A90: [Post-marketing]

An additional report may be made only for the reason that a re-examination code has been given for reports of adverse reactions, etc. in Japan. In additional reports, enter "2 = Amendment" in "C.1.11.1 Report Nullification / Amendment" and state that an additional report is being made because a re-examination code has been assigned in "C.1.11.2 Reason for Nullification / Amendment."

For reports of overseas adverse reactions, etc., research reports, or reports of actions taken, it is acceptable to use the re-examination code when making an additional report for different reasons after the re-examination code is assigned.

(8) Questions related to receipt

Q91: [Post-marketing]

If an adverse reaction occurs when a drug available in Japan is used during overseas travel, or if an adverse reaction occurs when a drug privately imported from overseas is used, which should be reported, a "report of adverse reactions, etc. in Japan" or a "report of overseas adverse reactions, etc."?

A91: [Post-marketing]

Reports shall be divided depending on the product used, regardless of where the adverse reaction occurred.

(1) If a marketing authorization holder becomes aware of an adverse reaction that occurred as a result of use of an in-house drug that was taken abroad, it should be reported as a "report of adverse reactions, etc. in Japan." For example, the case where an adverse reaction occurs when a drug available in Japan is used during overseas travel is applicable.

(2) If a marketing authorization holder becomes aware of an adverse reaction that occurred when a drug with the same ingredient as an in-house drug that is manufactured and marketed overseas (foreign pharmaceutical) was brought in Japan and used, it should be reported as a “report of overseas adverse reaction cases." For example, the case where an adverse reaction occurs when a drug privately imported from overseas is used is applicable.

Q92: [Clinical trial]
When an overseas sponsor is conducting the clinical trial by appointing the clinical trial in-country representative, can the clinical trial in-country representative report adverse reactions, etc. related to study drugs?

A92: [Clinical trial]
The clinical trial in-country representative shall report them.

Q93: [Post-marketing] [Clinical trial]
Is it acceptable for multiple companies in Japan to jointly report individual cases that occurred overseas? (For example, is it possible for Company A and Company B to report an adverse reaction caused by a combination drug jointly, or for two companies selling one product with two names [co-developed product] or two companies jointly developing one product to report the same case of adverse reaction, etc. [a case report in overseas literature]?)

A93: [Post-marketing] [Clinical trial]
As joint reports cannot be made in electronic reporting for reasons associated with electronic signature, etc., each company should make a report of adverse reactions, etc. individually. Similarly, joint reports cannot be made in reporting by CD, etc. Therefore, each company should make a report of adverse reactions, etc. individually. In each company's report, the same value shall be entered in “C.1.8.1 Worldwide Unique Case Identification Number” whenever possible.

Q94: [Post-marketing] [Clinical trial]
If a double-blind clinical trial of a new drug (before approval) of Company A has been conducted using a drug already marketed by Company B as a comparator, and unblinding has revealed that the comparator is the cause of an adverse reaction, which company, Company A or Company B, should report it, and how should it be reported?

A94: [Post-marketing] [Clinical trial]
Company A shall report it as a “report of adverse reactions, etc. in clinical trials.” In addition, Company A shall notify Company B that an adverse reaction was caused by the comparator, and Company B shall report the events as a “post-marketing report of adverse reactions, etc.” if it meets the reporting requirements.

Q95: [Post-marketing] [Clinical trial]
When a clinical trial is being conducted for the application for approval of partial changes in indications or dosage and administration of a drug that has already been marketed in Japan,
(1) If an adverse reaction/infection associated with the test drug concerned occurs in the clinical trial in Japan, should it be reported as a "post-marketing report of adverse reactions, etc." or as a “report of adverse reactions, etc. in clinical trials"?
(2) If an adverse reaction/infection associated with a drug with the same ingredient as that of the drug concerned occurs overseas, how should it be reported?
(3) How should research reports and foreign corrective action reports be made?

A95:

[Post-marketing]

(1) Adverse reactions/infections caused by test drugs in clinical trials in Japan do not fall under the provisions of Article 228-20 of the Regulation and therefore do not need to be reported as "post-marketing reports of adverse reactions, etc."
(2) It should be reported based on provisions of Article 228-20 of the Regulation.
(3) They should be reported based on provisions of Article 228-20 of the Regulation.

[Clinical trial]

(1) Adverse reactions/infections caused by test drugs in clinical trials in Japan fall under the provisions of Article 273 of the Regulation and therefore should be reported as "reports of adverse reactions, etc. in clinical trials."
(2) The event does not need to be reported because it corresponds to the provisions of Article 273, Paragraph 3 of the Regulation.
(3) They should be reported based on the provisions of Article 273 of the Regulation. In addition, similar actions in Japan should be reported as "foreign corrective action reports in clinical trials," and they should be stated in "J2.11 Other Reference Matters, etc." that these are the measures taken in Japan.

Q96: [Post-marketing] [Clinical trial]
What should be done if new information is obtained after a completion report?

A96: [Post-marketing] [Clinical trial]

If the change/addition is judged to affect the evaluation, a completion report shall be submitted again.

Q97: [Post-marketing]
Regarding the reports of adverse reactions, etc. for which the registration number or identification number had already been given on or before October 26, 2003 (i.e., before the date on which electronic reporting became available), how should the registration number or identification number be entered when an additional report is made on or after October 27, 2003?

A97: [Post-marketing]

When making an additional report on or after October 27, 2003, handle it as a new report and leave "J2.1b Identification Number (Number)" blank. As for the identification number and registration number given on or before October 26, 2003, provide the identification number in "C.1.9.1.r.2 Case Identifier(s)" and the registration number in "J2.11 Other Reference Matters, etc." When entering the identification number in "C.1.9.1.r.2," enter "true" in "C.1.9.1 Other Case Identifiers in Previous Transmissions," and "MHLW" in "C.1.9.1.r.1 Source(s) of the Case Identifier."

Q98: [Post-marketing] [Clinical trial]
In reporting the same case, is it acceptable to change the means of reporting, for example, using paper-based reporting for the initial report and electronic reporting for the second and subsequent reports?

A98: [Post-marketing] [Clinical trial]

For the same case, the means of additional reporting may be changed at each time.

Q99: [Post-marketing] [Clinical trial]

Regarding adverse reactions in Japan that occurred around the approval date, how should it be judged whether they should be reported as “reports of adverse reactions, etc. in clinical trials” or “post-marketing reports of adverse reactions, etc."?

A99: [Post-marketing] [Clinical trial]

It should be judged based on the approval status of the product concerned/test drug in Japan at the date and time of onset of the adverse reaction.

(1) Adverse reactions that occurred before the approval date should be reported as “reports of adverse reactions, etc. in clinical trials” based on provisions of Article 273 of the Regulation.

(2) Additional information on adverse reactions that occurred before the approval date should be reported in additional reports as “reports of adverse reactions, etc. in clinical trials.” In this regard, enter “8 = Other” in “J2.13.r.3 Development Phase,” and the phrase, “After approval,” and the “brand name” in “J2.11 Other Reference Matters, etc.”

(3) Adverse reactions that occurred on or after the approval date should be reported as “post-marketing reports of adverse reactions, etc.” based on the provisions of Article 228-20 of the Regulation. Moreover, the information on other adverse reactions which newly occurred on or after the approval date in patients who were reported in “reports of adverse reactions, etc. in clinical trials” before the approval date should be reported in initial reports also as “post-marketing reports of adverse reactions, etc.” In these reports, necessary information shall be entered with reference to Q&A 60 and 61. If an additional report in (2) and a report of another adverse reaction that newly occurred on or after the approval date are to be submitted at the same time, they may be reported together as a “post-marketing report of adverse reactions, etc.”

Q100: [Post-marketing] [Clinical trial]

Regarding overseas adverse reactions that occurred around the approval date, how should it be judged whether they should be reported as “reports of adverse reactions, etc. in clinical trials” or “post-marketing reports of adverse reactions, etc.”?

A100: [Post-marketing] [Clinical trial]

It should be judged based on the approval status of the product concerned in Japan at the time when the information is obtained.

(1) If the initial information is obtained before the approval date, it should be reported as a “report of adverse reactions, etc. in clinical trials” based on the provisions of Article 273 of the Regulation. If additional information on the case concerned is obtained on or after the approval date, the initial report shall be newly made as a “post-marketing report of adverse reactions, etc.” based on the provisions of Article 228-20 of the Regulation. In this regard, enter necessary information referring to Q&A 60 and 61.

(2) If the first information is obtained on or after the approval date, the initial report shall be made as a “post-marketing report of adverse reactions, etc.”

Q101: [Post-marketing] [Clinical trial]

Is it necessary to enter “C.1.11 Report Nullification / Amendment” in an additional report for a report of adverse reactions, etc.?

A101: [Post-marketing] [Clinical trial]

In E2B (R3) Implementation Guide, it is stated that “C.1.11” should be used to indicate that a previously transmitted report has been amended; however, it does not necessarily have to have a description in “C.1.11.1 Report Nullification / Amendment” and “C.1.11.2 Reason for Nullification / Amendment.”

When reporting the information not subject to reporting, it should not be made in “C.1.11.1” and “C.1.11.2” but in “J2.8.1 Flag for Not Subject to Reporting” and “J2.8.2 Reason for Not Subject to Reporting.”

Q102: [Post-marketing] [Clinical trial]

What should be done if the literature, etc. cannot be obtained after submission of a report with description of the literature titles, etc. in an attempt to obtain and send the submission data such as literature at a later date?

A102: [Post-marketing] [Clinical trial]

Make an additional report by stating in "J2.11 Other Reference Matters, etc." that the literature, etc. could not be obtained and entering "2 = Amendment" in "C.1.11.1 Report Nullification / Amendment" if there is no other information to be additionally reported.

Q103: [Post-marketing]

When multiple in-house drugs are suspected drugs in the same case, is it acceptable to prepare multiple reports for individual suspected drugs?

A103: [Post-marketing]

Do not prepare a report for each suspected drug, but report such case in one report. If different events occur in association with individual suspected drugs in one case, the time of onset differs greatly by event, and it is considered appropriate to handle them as different cases, multiple reports may be submitted.

Q104: [Clinical trial]

When multiple study drugs are suspected drugs in the same case, is it acceptable to prepare multiple reports for individual suspected drugs?

A104: [Clinical trial]

Do not prepare a report for each suspected drug, but report such case in one report. If different events occur in association with individual suspected drugs in one case, the time of onset differs greatly by event, and it is considered appropriate to handle them as different cases, multiple reports may be submitted.

Q105: [Clinical trial]

In 4. of the E2B (R3) Two Director Notification, it stated that "based on 'Handling of Notifications 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), for cases where a clinical trial notification was submitted according to previous rules, reports of adverse reactions, etc. in clinical trials should be made according to previous rules." What should be done if a report of adverse reactions, etc. has been made for each of the test drugs in the same case because multiple test drugs are used for suspected drugs, and additional reports are to be made on or after September 1, 2022?

A105: [Clinical trial]

For clinical trials for which a clinical trial notification or a notification of changes in clinical trial plan was submitted in the old format, it is allowed to make reports of adverse reactions, etc. in clinical trials according to the previous rules on or after September 1, 2022. However, note that if there is any change in the notification on or after September 1, 2022 and a clinical trial notification is submitted in a new format, adverse reactions, etc. need to be reported based on the E2B (R3) Two Director Notification.

For clinical trials for which a clinical trial notification or a notification of changes in clinical trial plan has been submitted in the old format, it is acceptable to submit one combined report as the additional report for the report of adverse reactions, etc. to the main test drug. In doing so, it is not necessary to withdraw the past reports regarding the test drugs other than the main test drug.

Q106: [Clinical trial]

In 4. of the E2B (R3) Two Director Notification, it stated that "based on 'Handling of Notifications 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), for cases where a clinical trial notification was submitted according to previous rules, reports of adverse reactions, etc. in clinical trials should be made according to the previous rules." Is it possible to make reports of adverse reactions, etc. based on the E2B (R3) Two Director Notification even if the clinical trial notification has been submitted according to the previous rules?

A106: [Clinical trial]

It is possible. If a notification has been submitted in the old format but a report on adverse reactions, etc. is made based on the E2B (R3) Two Director Notification, the drugs subject to reporting are test drugs.

Q107: [Clinical trial]

For study drugs other than the test drug entered at the time of switching a clinical trial notification or a notification of changes in clinical trial plan from the old format to the new format, is it necessary to report adverse reactions, etc. that have been obtained before the submission of a notification in the new format?

A107: [Clinical trial]

There is no need to report them.

Q108: [Clinical trial]

When the main test drug A and the test drug B which is not the main test drug have been notified in one notification and the cohorts related to the test drug B have been completed while the study related to the other test drug (the main test drug A) is ongoing, is a clinical trial completion notification related to the test drug B considered to have been submitted and is the period of mandatory reporting of adverse reactions, etc. to study drugs other than test drugs used in the cohorts related to the test drug B considered to have ended if a report of changes in clinical trial plan that the cohorts related to the study drug B are completed?

A108: [Clinical trial]

It is correct. When the cohorts related to the test drug B have been completed, a comment stating "The cohorts related to the test drug B have been completed. The study drugs other than test drugs used in the cohorts related to the test drug B are ●●●, ▲▲, and ■■." shall be included in the remarks column of the notification.

However, the information on the quantity of study drugs other than test drugs used in the cohorts related to the test drug B shall be entered when submitting the clinical trial completion notification or clinical trial discontinuation notification.

(9) Questions related to paper-based reporting

Q109: [Post-marketing]

When an initial report of adverse reactions, etc. is submitted by paper-based reporting, what items need to be stated in the attached forms of Post-marketing Director-General Notification?

A109: [Post-marketing]

Write at least "◎" (= items requiring description) shown in Appendices 1 and 2 of the E2B (R3) Two Director Notification. It is not necessary to write N data elements required for electronic reporting in the report.

Q110: [Post-marketing] [Clinical trial]
How should “E.i.3.2 Seriousness Criteria at Event Level” be entered in paper-based reporting?

A110: [Post-marketing] [Clinical trial]
Enter applicable ones among the following a to f in alphabet (multiple choices allowed).
a = Results in death
b = Life-threatening
c = Requiring inpatient hospitalization or prolongation of existing hospitalization for treatment
d = Results in persistent or significant disability/incapacity
e = Congenital anomaly
f = Other medically important conditions

Q111: [Post-marketing] [Clinical trial]
How should the elements other than “E.i.3.2 Seriousness Criteria at Event Level” shown in the above Q110 for which the value allowed is specified as "code value," “true," or "false" be written in the case of paper-based reporting?

A111: [Post-marketing] [Clinical trial]
Instead of entering “code value,” “true,” or “false” as they are, write the elements so that their contents are clearly understood from the report without referring to the code table, etc.

Q112: [Post-marketing] [Clinical trial]
MedDRA versions need to be entered in "D.7.1.r.1a MedDRA version for medical history," "D.8.r.7a MedDRA version of reaction," etc. For paper-based reporting, where should they be mentioned in the attached forms of Post-marketing Director-General Notification or Clinical Trial Director-General Notification?

A112: [Post-marketing] [Clinical trial]
Enter them in the "Remarks" column of Attached Form 1.

Q113: [Post-marketing] [Clinical trial]
According to Attachment 1 of the E2B (R3) Implementation Guide, “G.k.9.i.1 Reaction(s) / Event(s) assessed” is a technical reference element and not an element to be entered by the user. How should the information for “G.k.9.i.1 Reaction(s) / Event(s) Assessed” be entered in the attached forms of the Post-marketing Director-General Notification or Clinical Trial Director-General Notification in paper-based reporting?

A113: [Post-marketing] [Clinical trial]
Enter the names of adverse reactions/adverse events to be evaluated.

(10) Questions related to electronic reporting

Q114: [Post-marketing] [Clinical trial]
Regarding the application for the confirmation of connection with the management system for information on adverse drug reactions for the purpose of electronically reporting adverse reactions, etc., are there any set periods (including time) or days of the week during which the connection can be confirmed?

A114: [Post-marketing] [Clinical trial]
The connection shall be confirmed within business hours on business days of PMDA.

The details of the schedule will be notified by the Safety Report Management Division, Office of Informatics and Management for Safety, PMDA after the application.

Q115: [Post-marketing] [Clinical trial]
Does the unique number in the filename have to be the same as the company-specific tracking number entered in “N.1.2 Batch Number”?

A115: [Post-marketing] [Clinical trial]
Can be different.

Q116: [Post-marketing] [Clinical trial]
The electronic certificate is supposed to be by one of the representatives of the company (the president, etc.). Can the electronic signature of the responsible person appointed by the president be used?

A116: [Post-marketing] [Clinical trial]
Only the electronic certificates by company representatives shall be accepted.

Q117: [Post-marketing]
Should the same identifier as the sender identifier registered with PMDA for the purpose of reporting malfunctions, etc. of medical devices or regenerative medical products be registered?

A117: [Post-marketing]
The same one is desirable. However, a different sender identifier may be registered for each report only when it is inevitable for the sender to register the sender identifier for each report for administrative reasons.

Q118: [Post-marketing] [Clinical trial]
When reporting via the EDI tool (AS1 or AS2 specifications), is it acceptable to register an e-mail address or URL that has already been registered as a dedicated e-mail address (AS1 specifications) for sending/receiving reports of malfunctions, etc. of medical devices or regenerative medical products or as the URL (AS2 specifications) of the EDI tool?

A118: [Post-marketing] [Clinical trial]
Register the e-mail address dedicated to transmission/reception or the URL of the EDI tool for each report type among the reports of adverse reactions, etc. to drugs, quasi-drugs, and cosmetics and reports of malfunctions, etc. of medical devices or regenerative medical products excluding reports of malfunctions, etc. of medical devices and regenerative medical products during clinical trials (hereinafter referred to as "reports of adverse reactions, etc.”). However, if ACK files for different types of reports of adverse reactions, etc. can be received and processed without confusion by setting the EDI tool, the same e-mail address or URL may be registered.

Q119: [Post-marketing] [Clinical trial]
What should be done if electronic reporting cannot be made because of the shutdown of the management system for information on adverse drug reactions, the shutdown date is the reporting deadline, and paper-based reporting cannot be made on time due to reasons such as the distant location of the reporting company?

A119: [Post-marketing] [Clinical trial]

Contact the Information Management Section, Office of Informatics and Management for Safety, PMDA by phone, etc.

Q120: [Post-marketing] [Clinical trial]

When "AE" is entered in "ACK.A.4," "CA" is entered in "ACK.B.r.6," and an error code is entered in "ACK.B.r.7" among the elements for acknowledgement message in ACK files in electronic reporting, the report is classified as "Requiring additional report." Can the report be accepted?

A120: [Post-marketing] [Clinical trial]

It is accepted, but the error part should be corrected and the report shall be submitted as an additional report or a correction report.

Q121: [Post-marketing] [Clinical trial]

Regarding the "Registration Form for Person in Charge of Reporting of Adverse Reactions, etc. (new/changed)" for post-marketing phase and clinical trials, which personnel, the person in charge of practical operations of reporting of adverse reactions, etc. or the person in charge of the system for electronic reporting, is appropriate as the primary or secondary person in charge of reporting of adverse reactions, etc. to be registered?

A121: [Post-marketing] [Clinical trial]

The Registration Form for Person in Charge of Reporting of Adverse Reactions, etc. is used to communicate instructions for re-investigation of reported adverse reactions, etc., consideration of revision of "PRECAUTIONS," or submission, etc. of cumulative case reports of specific adverse reactions, etc. Therefore, two (primary and secondary) persons in charge of practical operations for reporting of adverse reactions, etc. should be registered with the Information Management Section, Office of Informatics and Management for Safety, PMDA. It is acceptable to have the same persons in charge of reporting of adverse reactions, etc. for post-marketing reporting and reporting in clinical trials.

Q122: [Post-marketing] [Clinical trial]

If the same case is re-transmitted (or re-submitted) on the same day, is it necessary to change the file name?

A122: [Post-marketing] [Clinical trial]

The file name should be changed for each transmission (or each submission).

When instructions are provided by PMDA, they should be prioritized.

Re-transmission should be done after confirming the receipt of ACK for the report sent initially.

Q123: [Post-marketing] [Clinical trial]

How is the expiration date of the electronic certificate related to the expiration date of the public key?

A123: [Post-marketing] [Clinical trial]

Once the expiration date of the electronic certificate has passed, the public key is no longer valid.

Q124: [Post-marketing] [Clinical trial]

What should be the file name when submitting the public key for reporters to PMDA?

A124: [Post-marketing] [Clinical trial]

The file name should be "sender identifier.cer."

Q125: [Post-marketing] [Clinical trial]
What procedures are needed if the public key of the authority expires?

A125: [Post-marketing] [Clinical trial]
PMDA will distribute new public keys to companies reporting electronically about 1 month before the expiration date. Each company should switch the key sequentially.

Q126: [Post-marketing] [Clinical trial]
What should be done when it is not possible to prepare the XML file by the reporting deadline because of the shutdown of in-house systems due to occurrence of natural disasters and other emergency circumstances, serious system failure, or other inevitable causes (e.g. computer virus infection)?

A126: [Post-marketing] [Clinical trial]
Each case will be handled separately. Contact the Information Management Section, Office of Informatics and Management for Safety, PMDA for post-marketing reporting, and the Review Planning Division, Office of Review Management, PMDA for reporting in clinical trials.

Q127: [Post-marketing] [Clinical trial]
The situations such as shutdown of the management system for information on adverse drug reactions because of natural disasters and other emergency circumstances are to be promptly notified through the representative e-mail addresses registered for post-marketing or clinical trial reporting or the PMDA's website. What should be done when the companies cannot confirm such situation because of no internet connection or similar circumstances?

A127: [Post-marketing] [Clinical trial]
Contact the Information Management Section, Office of Informatics and Management for Safety, PMDA by phone, etc.

Q128: [Post-marketing] [Clinical trial]
If there is no problem in the parse check, will all data written in XML be incorporated into the management system for information on adverse drug reactions as reported information?

A128: [Post-marketing] [Clinical trial]
In the management system for information on adverse drug reactions, only the items corresponding to XPath written in the notification are regarded as reported information. For J data elements, each element should be created with XML in accordance with XPath written in Appendix 4 of the E2B (R3) Two Director Notification. For E2B (R3) data elements, each element should be created with XML in accordance with XPath written in Attachment 3 of the E2B (R3) Implementation Guide.

Q129: [Post-marketing] [Clinical trial]
In Appendix 2 of the E2B (R3) Two Director Notification, it stated that "F.r.3.3 Test Result (unit)" should be written in the format of standard UCUM. Please show the specific check format.

A129: [Post-marketing] [Clinical trial]
The management system for information on adverse drug reactions checks whether the format of UCUM complies with the syntax rules defined in UCUM. For details of the rules and samples, etc. of acceptable UCUM codes, see the following URL.
https://unitsofmeasure.org/trac/

Q130: [Clinical trial]

When making an additional report according to the E2B (R3) Two Director Notification for a report made with "4 = Bioequivalence study," "5 = Clinical pharmacology study," or "6 = Preparing application" in "J.12.i.2 Development Phase" according to the E2B (R2) Two Director Notification, what code should be entered for "J2.13.r.3 Development Phase"?

A130: [Clinical trial]

If any development phase in accordance with the E2B (R3) Two Director Notification is applicable, enter the applicable code. If there is nothing, enter "8 = Other."

For the development phase, information on the main test drug shall be entered.

2. Immediate reports

Q131: [Post-marketing]

If, after an incompletion report of an adverse reaction not expected from necessary precautions, etc., "death" suspected to be caused by the adverse reaction based on the additional information is discovered, is it necessary to make an immediate report at the time of discovery?

A131: [Post-marketing]

An immediate report should be submitted. If an immediate report has been made by fax, the report specified in Article 228-20, Paragraph 1, Item 1 of the Regulation shall be made separately.

Q132: [Post-marketing]

If, after an immediate report is submitted by fax, the causal relationship with the suspected drug concerned is ruled out or it is found that the drug concerned was not administered, before the report specified in Article 228-20, Paragraph 1, Item 1 of the Regulation is made, or other similar cases arise, how should such a situation be handled?

A132: [Post-marketing]

Inform the Office of Pharmacovigilance I or Office of Pharmacovigilance II (Medical Device Safety Division, Office of Manufacturing Quality and Vigilance for Medical Devices for in vitro diagnostics) of PMDA of this by fax.

Q133: [Post-marketing]

In the Post-marketing Director-General Notification, it states, "For the observed cases of death in Japan suspected to have been caused by unknown adverse reactions, the initial report should be promptly made by fax, etc." On the other hand, in the E2D Guideline, it states, "unless the possibility of fatal outcome is clearly specified, the adverse reaction concerned with fatal outcome should be considered an unexpected adverse reaction." How should the events subject to immediate reporting be considered?

A133: [Post-marketing]

As in the past, deaths suspected of being caused by adverse reactions the occurrence of which itself is unknown are subject to immediate reporting. For adverse reactions handled based on the E2D Guideline as "unknown" because the possibility of fatal outcome associated with these reactions is not clearly stated in the sections of "Important Precautions," "Clinically significant adverse reactions," etc. even if they are listed in "Clinically significant adverse reactions," etc., it is not necessary to make immediate reports on deaths suspected of being caused by these adverse reactions.

As in the past, any case of infection should be immediately reported regardless of whether it is unknown or known.

3. Research reports/foreign corrective action reports

(1) Precautions common to research reports and foreign corrective action reports

Q134: [Post-marketing]
When a research report or a foreign corrective action report is submitted as one report for multiple products concerned, is it acceptable to write all products concerned using repetition in "G.k Drug(s) Information (repeat as necessary)"?

A134: [Post-marketing]
It is acceptable.

Q135: [Post-marketing] [Clinical trial]
Is it necessary to submit all materials held by the reporting company for research reports or foreign corrective action reports?

A135: [Post-marketing] [Clinical trial]
There is no need to submit all the materials held by the company. However, the literature, CCDS, etc. need to be submitted regardless of whether it is published or unpublished.

Q136: [Post-marketing] [Clinical trial]
If information to be reported is obtained around the approval date, how should it be judged whether to report the information as a "clinical trial research/foreign corrective action report" or as a "post-marketing research/foreign corrective action report"?

A136: [Post-marketing] [Clinical trial]
It should be judged based on the approval status of the product concerned in Japan at the time when the information is obtained.

(1) If the initial information is obtained before the approval date, it should be reported as a "clinical trial research/foreign corrective action report" based on the provisions of Article 273 of the Regulation. If additional information on the report concerned is obtained on or after the approval date, the initial report shall be newly made as a "post-marketing research/foreign corrective action report" based on the provisions of Article 228-20 of the Regulation. In this regard, enter necessary information referring to Q&A 137 and 138.

(2) If the first information is obtained on or after the approval date, the initial report shall be made as a "post-marketing research/foreign corrective action report."

Q137: [Post-marketing] [Clinical trial]
When the content reported as a "clinical trial research/foreign corrective action report" is reported as a "post-marketing research/foreign corrective action report," is it absolutely necessary to enter the identifier of each report in "C.1.8.1. Worldwide Unique Case Identification Number" and "C.1.10.r Identification Number of the Report Which Is Linked to This Report"?

A137: [Post-marketing] [Clinical trial]
"C.1.8.1" should be the same identifier for the "post-marketing research/foreign corrective action report" and the "clinical trial research/foreign corrective action report," and the identifier in each report should be entered in "C.1.10.r" where possible. In addition, in "J2.11 Other Reference Matters, etc.," it shall state that the "clinical trial research/foreign corrective action report" (or the "post-marketing research/foreign corrective action report") has already been submitted or is scheduled to be submitted, and if it has already been submitted, "J2.1 Identification Number" of the report concerned shall also be entered.

Q138: [Post-marketing] [Clinical trial]

When the content reported as a “clinical trial research/foreign corrective action report” is reported as a “post-marketing research/foreign corrective action report,” should the same value be used for the company’s unique case report number, etc. (“C.1.1 Sender's (Case) Safety Report Unique Identifier" and “N.2.r.1 Message Identifier”) when reporting as a “clinical trial research/foreign corrective action report” and when reporting as a “post-marketing research/foreign corrective action report”? Or, should different values be used?

A138: [Post-marketing] [Clinical trial]

Different values should be used.

(2) Research reports

Q139: [Post-marketing]

The Post-marketing Director-General Notification mentions research reports that “there is a risk of cancer or other serious diseases, disabilities, or death associated with adverse reactions to the drug or foreign pharmaceutical concerned or infections caused by their use.” What kind of reports are included in them?

A139: [Post-marketing]

They includes research reports, etc. indicating that there is a risk of disorders such as cancer, deafness, and blindness or death associated with the ingredients contained in the drug concerned.

The research reports include the ones published in academic journals, etc. in Japan or overseas or published or unpublished reports of research conducted by the marketing authorization holder of the drug concerned or its related companies. Specifically, reports of epidemiological surveys (or tabulation/analysis of adverse reactions), results of studies in animals, etc., and results of physical or chemical tests are included.

Q140: [Post-marketing] [Clinical trial]

When making a “research report that shows that there is no approved efficacy/effect” (for clinical trials, a “research report showing that there is no efficacy/effect for the disease investigated in the clinical trial”), which report should be made, an “infection research report” or an “adverse reaction research report”?

A140: [Post-marketing] [Clinical trial]

Report as an “adverse reaction research report.”

Q141: [Post-marketing] [Clinical trial]

When reporting the results of animal experiments as a research report, what should be selected for “C.1.3 Type of Report”?

A141: [Post-marketing] [Clinical trial]

Select “2 = Report from study.”

Q142: [Post-marketing] [Clinical trial]

Of the published literature, should case reports be submitted as reports of adverse reaction or infection cases, or research reports?

A142: [Post-marketing] [Clinical trial]

Case reports containing the information shown in "3.3.1 Minimum Information" in Attachment 1 of the E2B (R3) Implementation Guide should be submitted as reports of adverse reaction or infection cases.

However, published literature including the information indicating that the tendency of occurrence of adverse reactions or infections has significantly changed or that the drug concerned does not have the approved efficacy or effect should be reported also as research reports.

Q143: [Post-marketing]

In research reports on quasi-drugs/cosmetics, how should "G.k.2.2 Medicinal Product Name as Reported by the Primary Source" be written if there are multiple products containing a specific ingredient?

A143: [Post-marketing]

When reporting information on a specific ingredient, all the applicable in-house products shall be stated, in principle. However, if there are many applicable products, a description such as "representative product name, etc." is acceptable for "G.k.2.2." In this case, obtain the code for reporting adverse reactions, etc. for the "representative product name, etc.," enter the code in the ICSR file, and enter the ingredient name in "G.k.2.3.r.1 Substance / Specified Substance Name."

(3) Foreign corrective action reports

Q144: [Post-marketing]

What kind of cases are anticipated for the following actions overseas that "prevent the occurrence or spread of public health hazards including discontinuation of manufacturing, import, or marketing, recall, and disposal"?

(1) Changes in indications or dosage and administration
(2) Discontinuation of manufacturing, import, and marketing
(3) Recall and disposal of products
(4) Revision of PRECAUTIONS (WARNINGS AND PRECAUTIONS, etc.)
(5) Suspension of clinical trials

A144: [Post-marketing]

The following cases correspond to actions taken overseas.

(1) Changes in indications or dosage and administration where restrictions are placed for efficacy or safety reasons. Expansion of indications or dosage and administration is not a case to be reported.
(2) Discontinuation of manufacturing, import, or marketing or changes in manufacturing methods, etc. for efficacy or safety reasons (e.g., introduction of an inactivation process to prevent viral contamination in blood products). Discontinuation of manufacturing, import, or marketing and changes in manufacturing methods, etc. only for business reasons are not cases to be reported.

(3) Recall/disposal of products for efficacy or safety reasons, etc., including voluntary recall. Recall and disposal of products only for business reasons are not cases to be reported.
(4) Revision of PRECAUTIONS involving significant changes, etc.
(5) Suspension of the entire clinical trial due to safety problems.

Q145: [Clinical trial]
What kind of examples are there for the actions taken overseas that "prevent the occurrence or spread of public health hazards including discontinuation of manufacturing, import, or marketing, recall, and disposal"?

A145: [Clinical trial]
The following cases correspond to actions taken overseas.
(1) Changes of or restrictions on indications or dosage and administration for efficacy or safety reasons
(2) Discontinuation of manufacturing, import, or marketing or changes in manufacturing methods, etc. due to lack of efficacy or safety problems (e.g., introduction of an inactivation process to prevent viral contamination in blood products).
(3) Recall/disposal of products for efficacy or safety reasons, etc. (including voluntary recall)
(4) Revision of PRECAUTIONS (WARNINGS AND PRECAUTIONS, etc.) involving significant changes, etc.
(5) Suspension/discontinuation of the entire clinical trial due to quality, efficacy or safety problems
(6) Strengthening, etc. of safety measures by distribution of doctor letters, etc. during clinical trials

Q146: [Post-marketing] [Clinical trial]
When a foreign regulatory authority, etc. provides information on efficacy, safety, proper use, etc., for example, information necessary to prevent or mitigate serious adverse reactions, serious adverse events, serious medical accidents, etc. regardless of whether or not they can be expected from necessary precautions, etc. or Investigator's Brochure, etc., should it be reported as a foreign corrective action report?
What kind of specific cases can be assumed?

A146: [Post-marketing] [Clinical trial]
It should be reported.
Provision of information by foreign regulatory authorities may include revision of PRECAUTIONS (WARNINGS AND PRECAUTIONS, etc.) and recall information.
Foreign corrective action reports include, for example, addition of a precaution about a serious adverse reaction to the "BOXED WARNING" section in the U.S. Drug Labeling. When information on revision of PRECAUTIONS is obtained, it should be judged if it is subject to reporting of foreign corrective actions after appropriately evaluating whether it is the "information necessary to prevent or mitigate serious adverse reactions, serious adverse events, serious medical accidents, etc."

Foreign regulatory authorities are not limited to those of the U.S. (mentioned above), EU, and U.K. If information on actions taken overseas is obtained from an overseas partner company, it should be handled in the same manner as stated above.

Q147: [Clinical trial]
What kind of cases are subject to reporting of foreign corrective actions related to study drugs other than test drugs?

A147: [Clinical trial]
The measures against quality, efficacy, and safety problems associated with the use of the drug in the clinical trial concerned that may cause or expand public health hazards are subject to reporting.

4. Periodic reports of unknown/non-serious adverse drug reactions

(1) Reporting method

Q148: [Post-marketing]
For "other drugs" which are not drugs subject to periodic safety update reporting, is it acceptable to report drugs with the same active ingredients with different routes of administration as one periodic report of unknown/non-serious adverse drug reactions?

A148: [Post-marketing]
Even if the drug contains the same active ingredient, if the route of administration is different, a separate report should be submitted. However, if the package insert (including electronic package insert) is the same, it is acceptable to submit one report all together.

Q149: [Post-marketing]
For products with multiple approval dates, etc. due to addition of indications, different strengths, etc., is it acceptable to report them together in one periodic report of unknown/non-serious adverse drug reactions?

A149: [Post-marketing]
It is acceptable. In this case, among the approval dates, etc. of additional indications or different strengths, the approval date, etc. corresponding to the earliest date of submission shall be the base date for reporting on or after April 1, 2005.

Q150: [Post-marketing]
In the case of over-the-counter drugs, is it acceptable to submit one periodic report of unknown/non-serious adverse drug reactions for drugs with the same ingredients and different contents?

A150: [Post-marketing]
Products with the same ingredients may be reported in one report all together.

Q151: [Post-marketing]
For over-the-counter cold medicines, antipyretic analgesics, etc. that differ in only some of the active ingredients, is it acceptable to submit one periodic report of unknown/non-serious adverse drug reactions all together?

A151: [Post-marketing]

For drugs such as cold remedies and antipyretic analgesics for which approval standards for manufacturing (import) have been established, if the types, etc. of main active ingredients that must be combined are the same and the marketing authorization holder of the drugs concerned judges it appropriate to simultaneously take safety assurance measures such as revision of "PRECAUTIONS" in information on precautions, etc., it is acceptable to submit one report for multiple drugs combined.

In such a case, the reason for combining the drugs in one report shall be described in the "Remarks" column of Attached Form 7 of the Post-marketing Director-General Notification.

Q152: [Post-marketing]

When drugs with different strengths, dosage forms, etc. are reported together in one report, should the names of drugs without unknown/non-serious adverse reactions be included in the entry in the "Brand name" column, etc. in Attached Form 7?

A152: [Post-marketing]

Enter the names of all drugs investigated in the report, including the names of drugs without occurrence of unknown/non-serious adverse reactions during the reporting period.

Q153: [Post-marketing]

In the case of joint development products, is it acceptable to prepare and submit the periodic reports of unknown/non-serious adverse drug reactions jointly even after the end of the re-examination period?

A153: [Post-marketing]

It is acceptable.

(2) Base date for reporting, etc.

Q154: [Post-marketing]

For drugs subject to periodic safety update reporting, is it acceptable to change the expiration date of the survey unit period so that it becomes an arbitrary survey unit period if it is considered necessary from the viewpoint of safety measures after the completion of periodic safety update reporting?

A154: [Post-marketing]

It is acceptable. However, for the initial report after the change, the survey unit period shall be one year or shorter, and the reason for the change shall be described in the remarks column. The subsequent reports shall be made every year.

For example, for products for which the survey unit period is from June 1 to May 31 of the next year, if the survey unit period is changed to April 1 to March 31 of the next year, reporting shall be made once for the survey unit period from June 1 to March 31 of the next year, and subsequently the report shall be made every year with the survey unit period of April 1 to March 31 of the next year.

If there is no information on adverse reactions that should be reported during the initial survey unit period after the change and no periodic reports of unknown/non-serious adverse drug reactions were submitted, the fact that there was no information on adverse reactions which should be reported during the previous survey unit period and the reason for the change in the survey unit period shall be described in the remarks column at the time of the next reporting.

Q155: [Post-marketing]

Is it acceptable to match the survey unit period for periodic reports of unknown/non-serious adverse drug reactions of a drug which contains the same active ingredient as that of a specific drug subject to periodic safety update reporting, Drug A, and for which simultaneous safety measures are appropriate, Product B, with the survey unit period of Drug A subject to periodic safety update reporting?

A155: [Post-marketing]

It is acceptable. However, if either product is under re-examination and has been approved within the past 2 years, the survey unit period should be half a year or shorter.

Q156: [Post-marketing]

For "other drugs" which are not drugs subject to periodic safety update reporting, what does "international birth date, approval date, etc. of the drug" which can be the base date for reporting specifically refer to?

A156: [Post-marketing]

- International birth date
- Approval date
- Base date for reporting for periodic safety update reports (when the base date for reporting concerned continues to be used after the end of the re-examination period of the drug subject to periodic safety update reporting)
- The date the marketing authorization holder specified when reporting by CD, etc.

are indicated.

Q157: [Post-marketing]

For "other drugs" which are not drugs subject to periodic safety update reporting, the international birth date, the approval date, etc. of the drug are to be regarded as the base date for reporting. When it is considered necessary from the viewpoint of safety measures, is it acceptable to change the expiration date of the survey unit period so that it becomes an arbitrary survey unit period?

A157: [Post-marketing]

It is acceptable. However, for the initial report after the change, such survey unit period shall be one year or shorter, and the reason for the change shall be described in the remarks column. The subsequent reports shall be made every year.

For example, for products for which the survey unit period is from June 1 to May 31 of the next year, if the survey unit period is changed to April 1 to March 31 of the next year, reporting shall be made once for the survey unit period from June 1 to March 31 of the next year, and subsequently the report shall be made every year with the survey unit period of April 1 to March 31 of the next year.

If there is no information on adverse reactions that should be reported during the initial survey unit period after the change and no periodic reports of unknown/non-serious adverse drug reactions were submitted, the fact that there was no information on adverse reactions that should be reported during the previous survey unit period and the reason for the change in the survey unit period shall be described in the remarks column at the time of the next reporting.

Q158: [Post-marketing]

As “other drugs” which are not drugs subject to periodic safety update reporting, the international birth date, approval date, etc. of the drugs have been reported as the base date for reporting. What should be done if there is a new base date for reporting because of addition of indications, etc.?

A158: [Post-marketing]

The survey unit period for periodic reports of unknown/non-serious adverse drug reactions is changed in line with the survey unit period for periodic safety update reports, but the survey unit period for periodic reports of unknown/non-serious adverse drug reactions before change should be 1 year or shorter. In this case, it is not necessary to change the “base date for reporting" column of the periodic reports of unknown/non-serious adverse drug reactions or to have a prior consultation with PMDA, but at the time of the initial report after the change, the reason for the change should be described in the remarks column of the report.

If there is no information on adverse reactions that should be reported during the initial survey unit period after the change and no periodic reports of unknown/non-serious adverse drug reactions were submitted, the fact that there was no information on adverse reactions that should be reported during the previous survey unit period and the reason for the above change in the survey unit period shall be described in the remarks column in the report at the time of the next reporting.

Q159: [Post-marketing]

If an approval application for a replacement new product is made according to measures to prevent medical accidents, etc., a new approval date and approval number will be given. In such a case, which date should be the base date for reporting?

A159: [Post-marketing]

When using the approval date as the base date, either the previous or new approval date can be the base date.

If the previous approval date is used as the base date for reporting, enter the new approval date and approval number as well as the fact that the approval for a replacement new product was obtained during the said survey unit period in the remarks column.

If the new approval date is used as the base date for reporting, the report based on the previous approval shall be made during the period up to the day before the approval of the replacement new product, and the fact that the report is being made in less than one year because of the application for the new replacement product shall be described in the remarks column. After that, reporting should be made based on the new approval date as the base date for reporting. If there is no information on adverse reactions that should be reported during the initial reporting period after the change of the base date and no periodic reports of unknown/non-serious reactions were submitted, the fact that there was no information on adverse reactions that should be reported during the previous survey unit period shall be described at the time of the next reporting. If the information on adverse reactions to the previously approved product is obtained on or after the new approval date, the adverse reactions shall be reported as those associated with the new approval.

Q160: [Post-marketing]

The deadline for submission of a periodic report of unknown/non-serious adverse reactions to PMDA for drugs subject to periodic safety update reporting is set as within 70 days after the expiration date of the survey period. How should the expiration date of the survey period be counted?

A160: [Post-marketing]

The deadline for submission of the report should be set by using the expiration date of the survey unit period as Day 0.

If the deadline for submission of the report falls on a non-business day of PMDA, the next business day should be regarded as the deadline for submission of the report.

(3) Reporting target

Q161: [Post-marketing]

What actions should be taken if:

(1) An adverse reaction that was reported in an individual case safety report is subject to periodic reporting of unknown/non-serious adverse drug reactions based on the additional information.

(2) An adverse reaction that was subject to periodic reporting of unknown/non-serious adverse drug reactions is no longer subject to reporting based on the additional information.

(3) An adverse reaction that was subject to periodic reporting of unknown/non-serious adverse drug reactions is subject to individual case safety reporting based on the additional information.

(4) An adverse reaction that was reported in a periodic report of unknown/non-serious adverse drug reactions is no longer subject to reporting based on the additional information.

(5) An adverse reaction that was reported in a periodic report of unknown/non-serious adverse drug reactions is subject to individual case safety reporting based on the additional information.

A161: [Post-marketing]

(1) Report it in a periodic report of unknown/non-serious adverse drug reactions.
For the individual case safety report, do not withdraw it, but report that the event is not subject to reporting. See Attachment 2 of the E2B (R3) Five Director Notification for specific description method.

(2) It is acceptable not to report it in a periodic report of unknown/non-serious adverse drug reactions.

(3) Report it in an individual case safety report within the reporting deadline concerned using the date on which the information that serves as the basis for judging the event to be subject to individual case safety reporting is obtained as the base date. In this regard, describe the background clearly in "J2.2.2 Comment on Base Date for Reporting."

(4) Neither withdrawal report nor replacement report is necessary for the periodic report of unknown/non-serious adverse drug reactions.

(5) Report it in an individual case safety report within the reporting deadline concerned using the date on which the information that serves as the basis for judging the event to be subject to individual case safety reporting is obtained as the base date. In this regard, describe the background clearly in "J2.2.2 Comment on Base Date for Reporting."

Q162: [Post-marketing]

What actions should be taken in the following situations?

(1) If a case has been reported in a periodic report of unknown/non-serious adverse drug reactions during the survey unit period concerned and then the relationship is ruled out during the next survey unit period, is it necessary to describe this at the time of the next report?

(2) If a case that has been reported in a periodic report of unknown/non-serious adverse drug reactions during the survey unit period concerned remains to be an unknown/non-serious case and additional information is obtained during the next survey unit period, is it necessary to make a periodic report of unknown/non-serious adverse drug reactions again?

(3) If a case has been reported in a periodic report of unknown/non-serious adverse drug reactions during the survey unit period concerned, and occurrence of a new unknown/non-serious adverse reaction in this case is discovered based on the additional information, is it necessary to report it in a periodic report of unknown/non-serious adverse drug reactions?

A162: [Post-marketing]

Handle these situations as follows.

(1) There is no need to describe it.

(2) If there is no change in the judgment of seriousness, reporting is not required.
(3) The new unknown/non-serious adverse reaction needs to be reported.

Q163: [Post-marketing]
When an unknown/serious adverse reaction and an unknown/non-serious adverse reaction occur and an individual case safety report for the unknown/serious reaction is made including the name of the unknown/non-serious adverse reaction, is a separate periodic report of unknown/non-serious adverse drug reactions necessary?

A163: [Post-marketing]
It is necessary.

Q164: [Post-marketing]
What actions should be taken in the following situations?
(1) The non-proprietary name is identified but the product name is not identified.
(2) The marketing authorization holder of the product concerned and the product name are identified but the specification, dosage form, and route of administration are not identified.

A164: [Post-marketing]
Make reports as follows.
(1) Handle the product as an in-house product and make a report as a periodic report of unknown/non-serious adverse drug reactions.
(2) Report as a product with the specification, dosage form, and route of administration considered to be most likely based on the information obtained.

Q165: [Post-marketing]
If additional information has been obtained on or after April 1, 2005 on a minor adverse reaction unexpected from the necessary precautions, etc., which is not subject to reporting under the old reporting criteria, but there is no particular change in the evaluation, is it necessary to report the adverse reaction concerned in a periodic report of unknown/non-serious adverse drug reactions?

A165: [Post-marketing]
Reporting is not necessary.

5. Handling of cases reported directly to the authorities

Q166: [Post-marketing]
Regarding the case information of adverse reactions, etc. the marketing authorization holder received from PMDA, is it necessary for the marketing authorization holder to report the information concerned again to PMDA as reports on adverse reactions, etc.?

A166: [Post-marketing]
For case information on adverse reactions, etc. provided by PMDA, it is not necessary for the marketing authorization holder to make reports of adverse reactions, etc., in principle, but it is necessary to make these reports in the following cases:
[1] A case provided by PMDA not to be investigated in detail by PMDA that corresponds to the provisions of Article 228-20 of the Regulation

[2] Even if PMDA performs detailed investigation, when information on the same case which corresponds to the provisions of Article 228-20 of the Regulation (regardless of the amount of information) is obtained from sources other than PMDA, such as a medical institution and literature

[3] When additional information is obtained from sources other than PMDA, such as a medical institution and literature for a case being handled under the Relief Systems for Sufferers of Drugs and Infections Acquired through Biological Products provided by PMDA which corresponds to the provisions of Article 228-20 of the Regulation.

Q167: [Post-marketing]
The cases for which PMDA conducted detailed investigations are allowed to be used for safety measures. What should be done if the description of these cases as cases that provide basis is desired for the notification document at the time of revision of information on precautions, etc.?

A167: [Post-marketing]
If inclusion of these cases is desired, contact the Information Management Section, Office of Informatics and Management for Safety, PMDA in advance.

Q168: [Post-marketing]
For case information obtained from the information on reports of adverse reactions, etc. from patients published by PMDA, is it necessary for the marketing authorization holder to newly report this information to PMDA as a report of adverse reactions, etc.?

A168: [Post-marketing]
For cases corresponding to the provisions of Article 228-20 of the Regulation, the marketing authorization holder needs to report adverse reactions, etc. regardless of whether or not the cases are published by PMDA, when information on the same cases (regardless of the amount of information) other than the information on reports of adverse reactions, etc. from patients made public by PMDA is obtained from medical institutions, literature, etc.

However, if the information obtained by the marketing authorization holder does not contain any additional information other than the published information, it is not necessary to re-report adverse reactions, etc.

6. Long-term suspension of development, etc.

Q169: [Clinical trial]
To stop withholding and resume reporting of adverse reactions, etc., Attached Form 1 and 2 of "Points to Consider for Periodic Reporting of Cases of Clinical Trial Adverse Reactions, etc." (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) and the Development Safety Update Report (DSUR) are to be submitted along with the "Notification of Termination of Withholding of Reporting of Adverse Reaction/Infection Cases Associated with Investigational Products." What points should be noted?

A169: [Clinical trial]
The column for the number of reports should be left blank, and 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 reporting. For the Development Safety Update Report (DSUR), the reports for 1-year period up to the day before the latest base date for reporting may be attached.

When submitting the Notification of Termination of Withholding, contact the Review Planning Division, Office of Review Management, PMDA in advance.