

Q&A on Post-marketing Reports on Adverse Drug Reactions, etc. and Clinical Trial  
Reports on Adverse Drug Reactions, etc Conforming to Implementation Guide of E2B (R3)

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[Abbreviations]

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

Enforcement Ordinance: Ministerial Ordinance for Enforcement of Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Ordinance of the Ministry of Health and Welfare No. 1 of 1961)

Secretary-General Notification on Post-marketing: PFSD Notification No. 1002-20 by the Secretary-General of Pharmaceutical and Food Safety Bureau, MHLW, dated October 2, 2014, "Reports of Adverse Drug Reactions, etc. of Pharmaceuticals" (revised by PFSD Notification No. 1002-30 dated October 2, 2014)

Secretary-General Notification on Clinical Trial: PFSD Notification No. 0330001 by the Secretary-General of Pharmaceutical and Food Safety Bureau, MHLW, dated March 30, 2004, "Clinical Trial Reports of Adverse Drug Reactions, etc. in Clinical Trials to the PMDA" (revised by PFSD Notification No. 1215003 dated December 15, 2005 and PFSD Notification No. 1002 dated October 2, 2014)

E2B (R3) Two Directors' Notification: PFSB/ELD Notification No. 0917-1 and PFSB/SD Notification No. 0917-2, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, and by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 17, 2013, "Post-marketing Reports on Adverse Drug Reactions, etc and Clinical Trial Reports on Adverse Drug Reactions, etc. Conforming to Implementation Guide of E2B (R3)" (revised by PFSB/ELD Notification No. 0216-1 and PFSB/SD Notification No. 0216-2 dated February 16, 2015)

E2B (R2) Two Directors' Notification: PFSB/ELD Notification No. 0331002 and PFSB/SD Notification No. 0331009 by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, and by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 31, 2006, "Post-marketing Reports on Adverse Drug Reactions, etc and Clinical Trial Reports on Adverse Drug Reactions, etc." (This notification was abolished; however, the reports may be submitted in accordance with this notification until March 31, 2019. PFSB/ELD Notification No. 0917-1 and PFSB/SD Notification No. 0917-2 dated September 17, 2013)

E2B (R3) Three Office Directors' Notification: PMDA/ORM Notification No. 0216001, PMDA/OSI Notification No. 0216001, and PMDA/OSII Notification No. 0216001 by Director of Office of Review Management, Director of Office of Safety I, and Director of Office of Safety II, Pharmaceuticals and Medical Devices Agency, dated February 16, 2015, "Points to Consider in Post-marketing Reports on Adverse Drug Reactions, etc. and Clinical Trial Reports on Adverse Drug Reactions, etc."

ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Implementation Guide of E2B (R3): PFSB/ELD Notification No. 0708-5 and PFSB/SD Notification No. 0708-1, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau and by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated July 8, 2013, "Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs)" (revised by PFSB/ELD Notification No. 0202-1 and PFSB/SD Notification No. 0202-1, dated February 2, 2015)

E2B (R3) ICH Q&A: Administrative notice by Safety Division and Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated April 2, 2015, "Electronic Transmission of Individual Case Safety Reports (ICSRs) Questions & Answers"

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

Post-marketing report(s) on adverse drug reactions, etc.: Report(s) on adverse drug reactions, etc. provided in Article 68-10, Paragraph 1 of the Act

Clinical trial report(s) on adverse drug reactions, etc.: report(s) on adverse drug reactions, etc. related to clinical trials provided in Article 80-2, Paragraph 6 of the Act

PMDA: Pharmaceuticals and Medical Devices Agency

Electronic report(s): Report(s) using electronic data processing system

CD, etc. report(s): Report(s) submitted of CD-R (ROM) or DVD-R (ROM) in which the items listed in the attached forms of the Secretary-General Notification on Post-marketing or Secretary-General Notification on Clinical Trial are recorded and of documents in which the reporters' name, address, date of report, and other required items as specified in the Secretary-General Notification on Post-marketing or Secretary-General Notification on Clinical Trial

Paper report(s): Report(s) submitted in the form of document reports in which the required items specified in the attached forms of the Secretary-General Notification on Post-marketing and Secretary-General Notification on Clinical Trial are described and of CD-R (ROM) or DVD-R (ROM) in which the items listed in the attachment 1 "Data items for MHLW system management" and the attachment 2 "Data items for ICSR" in the Joint Notification of 2013 are recorded in XML format, which is supported in the Notification of Implementation Guide of E2B(R3)

Fax, etc. report(s): Report(s) which falls under the category of Section 2 (1) (ii) of the attachment of the Secretary-General Notification on Post-marketing

Files of ICSR, etc.: ICSR file and J item file

Former Reporting Standard: Provisions about the reports on adverse drug reactions, etc or reports on adverse drug reactions, etc in relation to clinical trials on drug substances

provided in Ordinance for Enforcement of Pharmaceutical Affairs Act before revision by the Ministerial Ordinance to Partially Revise the Ordinance for Enforcement of the Pharmaceutical Affairs Act (Ordinance of the Ministry of Health and Welfare No.30 of 2005)

MHLW: Ministry of Health, Labour and Welfare

## 1. Adverse Drug Reaction Reports and Infection Reports

### (1) Events to Be Reported

Q1: [Post-marketing] [Clinical trial]

Explain the scope of “cases suspected to be caused by adverse drug reactions.”

Should cases for which a causal relationship cannot be ruled out or is unknown be reported?

A1: [Post-marketing] [Clinical trial]

In ICH or other documents, an adverse drug reaction which is to be reported is defined as “an adverse event for which a causal relationship with the drug cannot be ruled out.” Currently in Japan, information is being collected on events in accordance with this definition.

“Cases suspected to be caused by adverse drug reactions” means cases other than “those for which a causal relationship can be ruled out.” “Cases for which causality is unknown” are also to be reported.

Q2: [Post-marketing] [Clinical trial]

Who determines whether a case is “suspected to be caused by adverse drug reactions”?

A2: [Post-marketing] [Clinical trial]

The sender shall determine based on the information on the evaluation of causality obtained from reporters. When reporting, the sender shall report cases other than those for which the sender and all the reporters determine that “a causal relationship can be ruled out.” If the reporters include “Lawyer” or “Consumer or other non-health professional” in addition to any of the “Physician,” “Pharmacist,” or “Other health professional,” the sender may assume that all the reporters rule out a causal relationship based on the fact that all the reporters of “Physician,” “Pharmacist,” or “Other health professional” ruled out a causal relationship.”

Q3: [Post-marketing]

Should an adverse drug reaction be considered serious when it requires hospitalization or prolongation of hospitalization for treatment of the adverse drug reaction, even if the reporters determined it as not serious?

A3: [Post-marketing]

It should be handled as a serious case.

Q4: [Post-marketing] [Clinical trial]

An infection caused by viral contamination was suspected but the viruses can only be detected by a testing method which is not currently fully recognized. In this case, should a report be submitted even if there are data that show no viral contamination obtained by a testing method which is currently recognized?

A4: [Post-marketing] [Clinical trial]

The case is to be reported. Infections suspected to be caused by the use of drugs shall be reported, regardless of whether or not a testing method for the virus has been established.

Q5: [Post-marketing]

Should an adverse drug reaction report be submitted for adverse drug reactions caused by defective drugs?

A5: [Post-marketing]

The adverse drug reaction report should be submitted even if the adverse drug reaction is caused by defective drugs.

Q6: [Post-marketing]

State whether or not the following are to be reported: a health hazard which was caused by something unrelated to the medical treatment, etc. of diseases, such as suicide, criminal act, or accidental ingestion by babies, infants, etc.

A6: [Post-marketing]

Such cases need not be reported based on the provision of Article 228-20 of the Enforcement Ordinance.

Q7: [Post-marketing]

The Secretary-General Notification on Post-marketing states that it is mandatory to report those cases which must be reported urgently to the government of the country where the cases occurred. What points should be noted specifically?

A7: [Post-marketing]

Note the following: regarding a drug which is marketed in Japan by a Japanese corporation and in foreign countries by alliance companies, when the alliance

companies report a case urgently to the government of the country where it occurred and the adverse drug reactions cannot be predicted from the Japanese Precautions, etc., the Japanese corporation shall also classify it as the unknown/serious case and report it.

Q8: [Post-marketing]

Explain what drugs are to be reported if they are used in foreign countries and are known to contain an ingredient that is equivalent to that contained in the drug concerned (approved in Japan).

A8: [Post-marketing]

- (1) If the ingredient of the drug is equivalent, the drug is to be reported even if the Indications, Dosage and Administration, other active ingredients in the case of combination product, etc. are different.
- (2) When the sender obtains approval for marketing in Japan of more than one drug product with same ingredients and becomes aware of a case of adverse drug reactions or infections overseas caused by the active ingredient, the sender shall submit a report on the drug product which is considered to be the most appropriate one among those for which approval for marketing in Japan has been granted and shall not omit reporting, in consideration of reason for use, dosage and administration, other active ingredients, etc. of the drug in question.
- (3) Regardless of whether or not the products are those of alliance companies overseas, if the ingredient is equivalent and information on adverse drug reactions, etc. which are serious and cannot be predicted from Precautions is obtained, the products are to be reported.

Q9: [Post-marketing] [Clinical trial]

Should a parent-child/fetus report be submitted in the case where the fetus was aborted due to occurrence of malformation, etc. considered to be caused by a drug or a test drug?

A9: [Post-marketing] [Clinical trial]

Such cases shall be submitted in the same form as a parent-child/fetus report.

Q10: [Clinical trial]

Is it permissible to exclude from reporting cases where the only purpose of hospitalization (planned surgery, tests, etc.) is to perform therapies or tests during a clinical trial which were planned before the trial?

A10: [Clinical trial]

Reporting in these cases is not required.

Q11: [Post-marketing]

Should infection reports be submitted when physicians report the following cases?

- (i) Viral hepatitis caused by blood products
- (ii) Sepsis associated with agranulocytosis
- (iii) Microbial substitution occurring as a result of the use of antibiotics
- (iv) Aseptic meningitis associated with vaccination
- (v) Methicillin-resistant *Staphylococcus aureus* (MRSA) infection during the use of antibiotics
- (vi) Emerging infectious disease during the use of drugs, etc.

A11: [Post-marketing]

- (1) Regarding (i) above, an infection report shall be submitted.
- (2) Regarding (ii) to (iv) above, reporting these as adverse drug reactions have usually been required. These cases shall be reported as heretofore.
- (3) Regarding (v) above, it is not necessary to submit a case report. However, consultation is to be arranged with the Office of Safety II, PMDA to ascertain whether or not information related to the mechanism of resistance, changes in incidence trends, etc. of the bacteria resistant to antibiotics associated with their use should be handled in the form of a research report.
- (4) Regarding (vi) above, an infection report shall be submitted. Detailed information on the symptoms, etc. of patients shall be investigated and evidence on which the diagnosis is based shall be verified, regardless of whether the case occurred in Japan or foreign countries.

If such a case occurs, consultation shall be sought with the Office of Safety II, PMDA.

Emerging infectious disease shall include HIV infection, etc.

(2) Reporting Time Frames, etc.

Q12: [Post-marketing]

Part 2 (2) of the Notification No. 25 by the Director of Safety Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated March 11, 1998, "Thoroughness of Safety Measures for Drugs" states that "Regarding adverse drug reactions to be newly described due to the revision of the package insert, when information similar to the adverse drug reactions is obtained between the revision of the package insert and the completion of transmitting information to medical institutions, etc., the case shall be handled as an 'adverse drug reaction which cannot be predicted from Precautions' and reported within 15 days." What does the "completion of transmitting information to medical institutions, etc." refer to in terms of timing?

A12: [Post-marketing]

It shall be the date of the completion of transmitting information performed by companies or the date of distribution of the “Drug Safety Update (DSU)” to the medical institutions, whichever is earlier.

Q13: [Post-marketing] [Clinical trial]

When submitting a post-marketing report on adverse drug reactions, etc., the case to be reported was considered as subject to reporting within 30 days. However, before submitting the first report, this report turned out to be one which should have been submitted within 15 days due to additional information. In this case, when does the reporting time frame end?

In addition, when submitting a clinical trial report on adverse drug reactions, etc., the case to be reported was considered as subject to reporting within 15 days. However, before submitting the first report, this report turned out to be one which should have been submitted within 7 days due to additional information. In this case, when does the reporting time frame end?

A13: [Post-marketing]

The report shall be submitted within 15 days from the day on which it turned out to be one that shall be submitted within 15 days, as the initial date. However, if 30 days have already elapsed from the day on which the information which was thought to be reported within 30 days of the reporting time frame was obtained, at least such information shall be reported within 30 days from the day on which the information was obtained, as the initial date.

[Clinical trial]

The report shall be submitted within 7 days from the day on which, it turned out to be one that shall be submitted within 7 days, as the initial date. However, if 15 days have already elapsed from the day on which the information which was thought to be reported within 15 days of the reporting time frame was obtained, at least such information shall be reported within 15 days from the day on which the information was obtained, as the initial date.

### (3) Predictability

Q14: [Post-marketing]

What items of “Precautions” are used to determine whether or not an adverse drug reaction is predictable?

A14: [Post-marketing]

The following items, which are listed in “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), are applicable.



“Warnings,” “Contraindications,” “Relative contraindications,” “Precautions related to indications,” “Precautions related to dosage and administration,” “Careful administration,” “Important precautions,” “Drug interactions,” “Adverse reactions,” “Use in the elderly,” “Use in pregnant, parturient, and nursing women,” “Use in children, etc.,” “Effects on laboratory tests,” “Overdosage,” and “Precautions in use.”

Q15: [Post-marketing]

Explain how to determine an adverse drug reaction which cannot be predicted from the descriptions in the “Precautions” section

A15: [Post-marketing]

It shall be determined based on section 2.4 Unexpected ADR in the E2D guideline, in consideration of Precautions.

Q16: [Post-marketing]

The Secretary-General Notification on Post-marketing states that “Adverse drug reactions that cannot be predicted from Precautions, etc.’ means those which are not described in ‘Warnings,’ ‘Important Precautions,’ ‘Drug interactions,’ ‘Adverse reactions,’ etc. of Precautions, etc.; or those whose nature, level of symptoms, specificity, etc. are not consistent with the descriptions even if they are described in Precautions, etc.” What adverse drug reactions are included in “those whose nature, level of symptoms, specificity, etc. are not consistent with the descriptions even if they are described in Precautions, etc.”?

A16: [Post-marketing]

For example, the following cases are applicable:

- (1) In the case of occurrence of an adverse drug reaction which has a name similar to that found in Precautions but has different severity or mechanism of onset. (for example, hepatitis” vs. “fulminant hepatitis” [when “hepatitis” was included in Precautions but “fulminant hepatitis” developed]; “anemia” vs. “aplastic anemia”; “leukopenia, erythropenia, thrombocytopenia” vs. “pancytopenia”; “leukopenia (granulocytopenia)” vs. “agranulocytosis”; and “diarrhea” vs. “diarrhea associated with dehydration and electrolyte abnormality”)
- (2) In the case of occurrence of a (limited) adverse drug reaction which is described more specifically than that described in Precautions (for example, “acute renal failure” vs. “interstitial nephritis”)
- (3) In cases associated with abnormal laboratory data as well as other symptoms despite the inclusion of descriptions of abnormal laboratory data (for example, “decreased serum potassium” vs. “decreased serum potassium associated with weakness and arrhythmia”)

Symptoms and signs which are usually associated with the adverse drug reactions described can be predicted from information contained in Precautions. (For example,

“shock” vs. “decreased blood pressure, increased heart rate, decreased urine output associated with shock”; and “aplastic anemia” vs. “pallor and fatigue associated with aplastic anemia”)

Q17: [Post-marketing]

Is it allowed to determine the predictability of adverse drug reactions reported in foreign countries based on the Precautions in the corresponding Japanese package insert?

A17: [Post-marketing]

Yes.

Q18: [Clinical trial]

The Secretary-General Notification on Clinical Trial states that “Adverse drug reactions that cannot be predicted from the investigator’s brochure’ refers to those which are not described in the investigator’s brochure; or those whose nature, level of symptoms, and onset tendency are not consistent with the descriptions even if they are described in the investigator’s brochure.” What are the adverse drug reactions “whose nature, level of symptoms, and onset tendency are not consistent with the descriptions even if they are described in the investigator’s brochure”?

A18: [Clinical trial]

As shown in PAB/ELD Notification No. 227 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated March 20, 1995, “Clinical Safety Data Management,” events which have a more specific (limited) description than those described in the investigator’s brochure or serious events that fall under the category of those which cannot be predicted.

For example, when “interstitial nephritis” is reported despite the description of “acute renal failure” in the investigator’s brochure, “interstitial nephritis” is determined as being unpredictable from the information contained in the investigator’s brochure.

The same should apply to the following cases: “hepatitis” vs. “fulminant hepatitis”; “anemia” vs. “aplastic anemia”; “leukopenia, erythropenia, thrombocytopenia” vs. “pancytopenia”; “leukopenia (granulocytopenia)” vs. “agranulocytosis”; “diarrhea” vs. “diarrhea associated with dehydration and electrolyte abnormality”; etc.

The same shall apply to cases associated with abnormal laboratory data as well as other symptoms despite the inclusion of descriptions of abnormal laboratory data (for example, “decreased serum potassium” vs. “decreased serum potassium associated with weakness and arrhythmia”).

Symptoms and signs which are usually associated with the adverse drug reactions described can be predicted from the information contained in the investigator’s brochure. (For example, “shock” vs. “decreased blood pressure, increased heart rate, decreased urine output associated with shock”; and “aplastic anemia” vs “pallor and fatigue associated with aplastic anemia”)

Q19: [Clinical trial]

An adverse drug reaction that occurred during a double-blind, controlled trial and was submitted in the “clinical trial report on adverse drug reactions, etc.” with blinding maintained and was also reported to medical institutions after incorporating it into the investigator’s brochure with blinding maintained. If the same adverse drug reaction should occur thereafter, which category does the adverse drug reaction fall into, predictable or unpredictable based on the investigator’s brochure?

A19: [Clinical trial]

When an adverse drug reaction was submitted in a “clinical trial report on adverse drug reactions, etc.” with blinding maintained and medical institutions were informed after incorporating the information the investigator’s brochure, the adverse drug reaction may thereafter be handled as one that can be predicted from the investigator’s brochure.

Q20: [Clinical trial]

If an adverse drug reaction is caused by a comparator and the information on the same adverse drug reaction cannot be obtained other than by breaking the blinding of a double-blind, controlled trial, should the adverse drug reaction be handled as one that cannot be predicted from the investigator’s brochure?

A20: [Clinical trial]

If an adverse drug reaction is caused by a comparator and the information on the same adverse drug reaction cannot be obtained except by unblinding, the adverse drug reaction shall be handled as one that cannot be predicted from the investigator’s brochure.

#### (4) Criteria for Severity

Q21: [Post-marketing]

When information on the occurrence of an adverse drug reaction is obtained but the information needed to evaluate the severity cannot be obtained, how should the case be treated?

A21: [Post-marketing]

Efforts should be made to collect detailed information so that the severity can be evaluated. The severity is to be evaluated based on the information obtained on the adverse drug reaction that has occurred.

Q22: [Post-marketing] [Clinical trial]

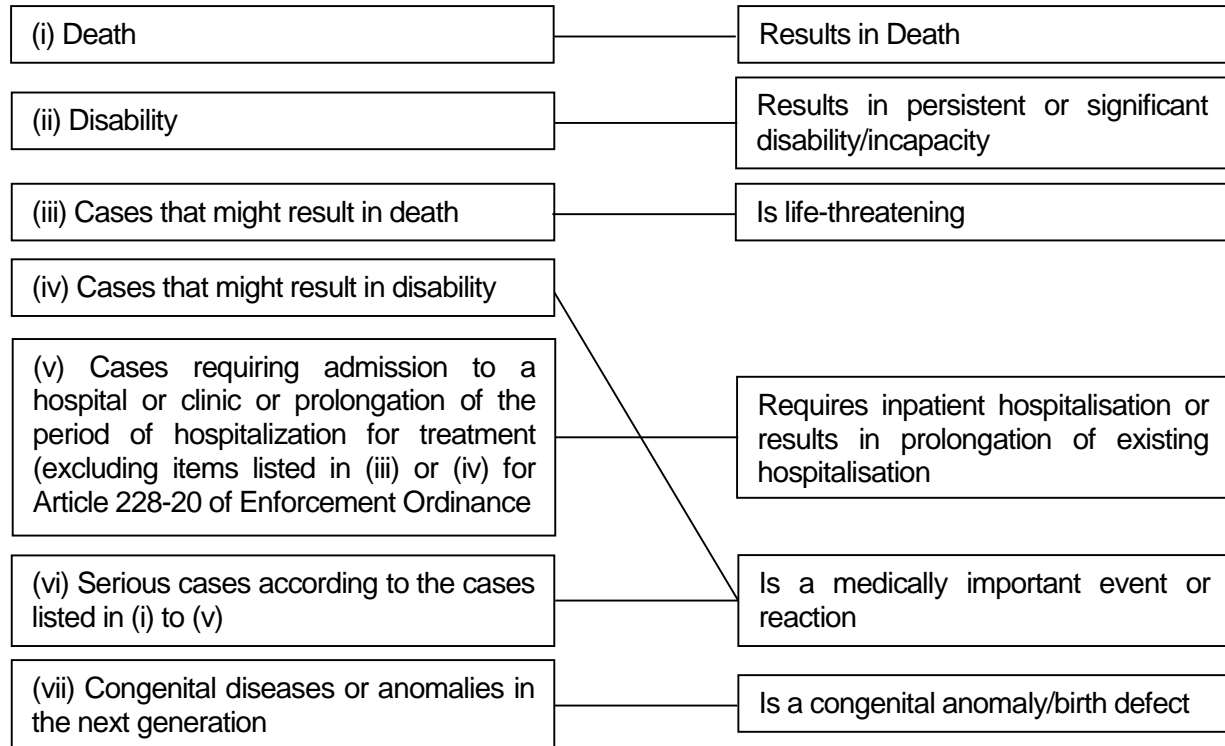
How should the definition of severity for adverse drug reactions in ICH be understood?

A22: [Post-marketing] [Clinical trial]

Refer to the following table.

Articles 228-20 and 273 of the Enforcement Ordinance

ICH



Q23: [Post-marketing]

How is “death” in Article 228-20 of the Enforcement Ordinance to be interpreted?

A23: [Post-marketing]

This refers to deaths that are suspected of being caused by adverse drug reactions. This falls under “Results in death” in the ICH provision (See E2D Guideline). For example, death following an infection caused by granulocytopenia, myelosuppression, etc., certainly falls into the category of a death for which an adverse drug reaction report is required. Where the sender determines that a death was caused by an adverse drug reaction, it shall be handled as a case of death, even if the reporters do not determine so.

Q24: [Post-marketing]

How is “disability” in Article 228-20 of the Enforcement Ordinance to be interpreted?

A24: [Post-marketing]

This refers to the onset of dysfunction to an extent which causes problems in daily life, and which falls into “Results in persistent or significant disability/incapacity” in the ICH provision (See E2D Guideline).

Q25: [Post-marketing]

How is the phrase “cases that might result in death” in Article 228-20 of the Enforcement Ordinance to be interpreted?

A25: [Post-marketing]

It falls into “Is life-threatening” in the ICH provision (See E2D Guideline) and refers to cases where a patient is at risk of death at the time of onset of the event. This does not refer to cases that might have resulted in death if they were more serious.

Q26: [Post-marketing]

How is the phrase “cases that might result in disability” in Article 228-20 of the Enforcement Ordinance to be interpreted?

A26: [Post-marketing]

This refers to cases where a patient was at risk of onset of dysfunction to a degree that causes problems in daily life when the adverse drug reaction occurred. It falls under “Is a medically important event or reaction” in the ICH provision (See E2D Guideline). This does not mean that the disability might have persisted if it were more serious.

Q27: [Post-marketing]

How is the phrase “cases requiring admission to a hospital or clinic or prolongation of the period of hospitalization for treatment” in Article 228-20 of the Enforcement Ordinance to be interpreted?

A27: [Post-marketing]

It falls under “Requires inpatient hospitalisation or results in prolongation of existing hospitalisation” in the ICH provision (See E2D Guideline). This refers to cases where hospitalization or prolonged hospitalization is required to treat adverse drug reactions, including the case where a patient is hospitalized to treat adverse drug reactions but receives no treatment (i.e., resting cure). For example, it includes hospitalization due to anaphylactic shock or pseudomembranous colitis. The following cases are excluded: hospitalization or prolongation of hospitalization to undergo testing, and hospitalization for follow-up despite the adverse drug reactions having resolved or are resolving.

Q28: [Post-marketing]

How is the phrase “death or serious cases according to the cases listed in (i) to (iii)” in Article 228-20, Paragraph 1, Item 1-(c)-(4) of the Enforcement Ordinance to be interpreted?

A28: [Post-marketing]

It falls under “a medically important event or reaction” in the ICH provision (See E2D Guideline). That is, it refers to critically 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 to prevent one of the other outcomes such as “results in death,” “results in persistent or significant disability/incapacity,” “life-threatening,” and “requires inpatient hospitalization or results in prolongation of existing hospitalization.” Examples of such events are intensive treatment in an emergency room, etc. or at home

for allergic bronchospasm; a case where a blood disorder or convulsions develop although it does not lead to hospitalization; or drug addiction or drug abuse.

Q29: [Post-marketing]

How should the phrase “congenital diseases or anomalies in the next generation” in Article 228-20 of the Enforcement Ordinance be interpreted.

A29: [Post-marketing]

It falls under “a congenital anomaly/birth defect” in the ICH provision (See E2D Guideline). It includes the case where it is suspected that anomalies in neonates have been caused by exposure to the drug before or during pregnancy. Examples of such events are organ hypoplasia of neonates caused by thalidomide, and vaginal cancer in female neonates caused by diethylstilbestrol.

Q30: [Post-marketing]

How are the “Criteria of Severity of Adverse Drug Reactions for Drugs, etc.” (PAB/SD Notification No. 80 issued by the Director of Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated June 29, 1992; hereinafter referred to as “Severity Criteria Notification”) to be applied when determining severity?

A30: [Post-marketing]

Severity shall be determined according to the definitions of severity for adverse drug reactions in ICH shown in the table in A22 above. The Severity Criteria Notification is only a guide for the sender to determine the level of symptoms. The severity shall not be determined solely based on the criteria used to grade the severity of an adverse reaction. (For example, a case for which only the laboratory data are classified as grade 3 does not mean that the case will invariably fall under the category of “serious.”)

#### (5) Instructions for Description

Q31: [Post-marketing]

Regarding the items which are listed in Attachments 1 and 2 of E2B (R3) Two Directors’ Notification and can be simply described, how should they be described?

A31: [Post-marketing]

It is mandatory to include these items when a completion report is submitted. Failure to include the items will result in an error report. Therefore, for example, if the descriptions of Precautions, etc. in the reports on known/serious adverse drug reactions (excluding cases of death) are included in “J2.11 Other References,” simple expressions, such as “described in the package insert,” are acceptable.

Q32: [Post-marketing] [Clinical trial]

Are there any precautions regarding the description of the time zone?

A32: [Post-marketing] [Clinical trial]

See the Appendix II of Implementation Guide of E2B (R3) for how to describe date/time. When checking the data between items, etc., be careful how these are handled because Japan Standard Time (+09:00) shall be used if there is no description of the time zone; if there is a description of the time zone, the time shall be converted into Japan Standard Time.

Q33: [Post-marketing] [Clinical trial]

Is it allowable to use double-byte characters for “NUM” and “date (minimum precision)” for the data type?

A33: [Post-marketing] [Clinical trial]

“NUM” and “date (minimum precision)” for the data type shall be entered using single-byte characters.

Q34: [Post-marketing] [Clinical trial]

Is it allowable to use characters with umlaut, etc. for “TXT” for the data type?

A34: [Post-marketing] [Clinical trial]

Characters with umlaut, etc. are acceptable provided the character string can be used in UTF-8. However, it is preferable not to use the characters with umlaut, etc. for Japanese cases. Character types such as “<” and “>”, which are not allowed in an XML message, cannot be used.

## (6) J Data Elements

Q35: [Post-marketing]

When the accumulated number of reports is entered in “J2.11 Other References,”

- (1) what type of adverse drug reactions, etc. are to be handled as related adverse drug reactions, etc.?
- (2) is it correct to assume that the accumulated number of reports (in Japan/overseas) refers to the number of cases reported to PMDA?
- (3) explain specifically how to describe when entering the number of reports in Japan for the past 3 years by year, when reporting a case of death in which an adverse drug reaction, etc. can be predicted from Precautions and for which a causal relationship with the adverse drug reaction, etc. cannot be ruled out.

A35: [Post-marketing]

- (1) The following cases shall be handled as related adverse drug reactions, etc.:  
Example 1: When reporting increased AST (GOT) and ALT (GPT), handle hepatic disorder and fulminant hepatitis as related adverse drug reactions, etc.

Example 2: When reporting granulocytopenia, handle agranulocytosis as the related adverse drug reaction, etc.

- (2) Enter the number of the adverse drug reaction reports and infection reports submitted to PMDA (excluding the number of unknown/minor adverse drug reactions; and the number of cases of unknown/nonserious adverse drug reactions on and after April 1, 2005) subtracting the number of reports which were withdrawn later and the number of reports on cases which were excluded from reporting.
- (3) Enter the number of cases of death for which a causal relationship with the adverse drug reactions, etc. reported to PMDA cannot be ruled out in “J2.11 Other References” as in the examples shown below.

Example 1: When reporting in each fiscal year

FY 2013, 2 cases

FY 2014, 1 case

FY 2015, 1 case (including this report)

Example 2: When reporting in each calendar year

January to December 2013, 2 cases

January to December 2014, 1 case

January to December 2015, 1 case (including this report)

Q36: [Post-marketing]

Regarding an adverse drug reaction which cannot be predicted from Precautions based on the E2D Guideline, because no clear statement in the sections such as “Warnings,” “Important precautions,” and “Clinically significant adverse reactions” that a fatal outcome may occur due to the adverse drug reaction, should the accumulated number of reports be submitted including this adverse drug reaction as an unknown adverse drug reaction?

A36: [Post-marketing]

As in the past, it is acceptable to enter the number of reports on cases of deaths in Japan for which a causal relationship with the adverse drug reactions etc. cannot be ruled out for the past 3 years by year.

It is not necessary to provide the “accumulated number of reports (in Japan/overseas)” on the adverse drug reactions and related adverse drug reactions that should be included when reporting the cases in Japan of adverse drug reactions which cannot be predicted from Precautions or when reporting the cases overseas of adverse drug reactions caused by new drugs, etc. within 1 year after their launch.

Q37: [Post-marketing]

Regarding drugs for which the early post-marketing phase vigilance is conducted again due to additional Indications, etc. during the re-examination period of drugs with new



active ingredients, when an adverse drug reaction occurs after completion of the early post-marketing phase vigilance even when used in accordance with the Indications, etc. and is subject to early post-marketing phase vigilance, which status type shall be selected to report “J2.4.k Status Type of New Drugs, etc.”?

A37: [Post-marketing]

For reporting, “within 2 years after approval” shall be selected if the case occurred within 2 years after the approval of additional Indications, etc.; or “not applicable” if the case occurred more than 2 years after the approval of additional Indications, etc. However, when the approval of the additional Indication, etc. is obtained after the termination of the re-examination period, “not applicable” shall be selected even if it occurred within 2 years after the approval.

Q38: [Clinical trial]

“J2.4.k Status Type of New Drugs, etc.” always requires the data entry in the first repetition when the type of report is “clinical trial.” What is the standard used to determine the first repetition?

A38: [Clinical trial]

“J2.4.k Status Type of New Drugs, etc.” has the same repetition unit as that in “G.k Drug(s) Information (repeat as necessary).” The management system for information on adverse drug reactions acquires the values using XPath. “J2.4.k” belonging to “G.k,” which is initially acquired using XPath, shall fall under the category of the first repetition.

Q39: [Post-marketing] [Clinical trial]

When both a marketed product and an investigational product are included as suspect drugs in the same case, is it correct to enter respective “J2.4.k Status Type of New Drugs, etc.”?

A39: [Post-marketing] [Clinical trial]

Yes.

## (7) ICSR Data Elements

Q40: [Post-marketing] [Clinical trial]

CCYYMMDDhhmmss shall be entered in “N.1.5 Date of Batch Transmission,” “N.2.r.4 Date of Message Creation,” and “C.1.2 Date of Creation.” Explain what to do when there is a time lag between the time the ICSR files, etc., were created and the time the data was transmitted.

A40: [Post-marketing] [Clinical trial]

“N.2.r.4” and “C.1.2” shall be completely coincident for the creation of ICSR files, etc. Date (CCYYMMDDhhmmss) of “N.1.5” shall be entered in consideration of the fact that it should be the time after the creation of “N.2.r.4.” Regarding an additional report, if the

date of “C.1.2” is the same as that of the previous report, an error will occur. Therefore, the date shall be entered taking into consideration that the date should be after that of the previous report.

If ICSR files are submitted using a CD, etc., it is acceptable to set mmss as “0000.”

Q41: [Post-marketing] [Clinical trial]

When a single company submits the same reports on adverse drug reactions, etc. caused by a suspect drug, is it necessary to set the “C.1.8.1 Worldwide Unique Case Identification Number” as the same value in each report on adverse drug reactions, etc.?

A41: [Post-marketing] [Clinical trial]

The number shall be the same.

Q42: [Clinical trial]

When two companies which are jointly developing the same drug respectively submit a report on adverse drug reactions, etc., is it possible for the company submitting the report earlier to inform the other company of “C.1.1. Sender’s (case) Safety Report Unique Identifier”?

A42: [Clinical trial]

It is preferable for the company submitting the report on adverse drug reactions, etc. earlier to advise the jointly developing company of the “C.1.1,” “C.1.8.1 Worldwide Unique Case Identification Number,” and other data using the ICSR file. When the company receiving the information creates ICSR files, etc., it shall enter informed “C.1.8.1” in the “C.1.8.1”; “true” in “C.1.9.1 Other Case Identifiers in Previous Transmissions”; partner organization name in “C.1.9.1.r.1 Source(s) of the Case Identifier”; and informed “C.1.1” in “C.1.9.1.r.2 Case Identifier(s).”

Q43: [Post-marketing] [Clinical trial]

If a report is submitted by mail, is it correct to indicate the dates for “N.1.5 Date of Batch Transmission,” “N.2.r.4 Date of Message Creation,” and “C.1.2 Date of Creation” as the date on which the mail was sent?

A43: [Post-marketing] [Clinical trial]

Yes. If ICSR files are submitted using a CD, etc., it is acceptable to set mmss as “0000.”

Q44: [Post-marketing] [Clinical trial]

In submitting more than one report on a suspect drug, when an own concomitant drug is also a suspect drug in addition to the drug subject to testing, investigation, etc., which should be selected for “C.1.3 Type of Report” for the drug, “1 = Spontaneous report” or “2 = Report from study”?

A44: [Post-marketing] [Clinical trial]

It is correct to enter “2” in “C.1.3.”

Q45: [Post-marketing]

For a report on an own drug 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”?

A45: [Post-marketing]

Yes.

Q46: [Post-marketing] [Clinical trial]

A reporter suspected that an infectious disease could have been caused by a drug or test drug and conveyed this information to a medical representative, etc., but will endeavor to make a final determination after seeing the result of another test (viral marker). In this case, is it allowable to set “C.1.4 Date Report Was First Received from Source” as the date when the reporter made the final determination after seeing the result of the other test?

A46: [Post-marketing] [Clinical trial]

It shall be the date on which the reporter advised the medical representative, etc. of the possibility that the infectious disease could have been caused by the drug or test drug.

Q47: [Post-marketing]

If a marketing authorization holder partially outsources the post-marketing safety management services, is it allowable to set the date when the marketing authorization holder obtains the information from the outsourcee as “C.1.4 Date Report Was First Received from Source”?

A47: [Post-marketing]

“C.1.4” shall be handled as the date when the marketing authorization holder or the outsourcee obtains the information, whichever is earlier.

Q48: [Post-marketing] [Clinical trial]

When a same case overseas is submitted as both the “post-marketing report on adverse drug reaction, etc.” and “clinical trial report on adverse drug reaction, etc.” is it necessary to enter the identification numbers of each report in “C.1.10.r Identification Number of the Report Which Is Linked to This Report”?

A48: [Post-marketing] [Clinical trial]

If possible, the identification numbers of each report should be entered in “C.1.10.r,” and the fact that the case has already been or will be submitted in the “post-marketing report on adverse drug reactions, etc. overseas” (or “clinical trial report on adverse drug reactions, etc. overseas”) should be entered in “J2.11 Other References.”

Q49: [Post-marketing] [Clinical trial]

When a same case overseas is submitted as both the “post-marketing report on adverse drug reaction” and “clinical trial report on adverse drug reaction,” which shall be used, the same or a different number for the company-unique case report number, etc. (“C.1.1 Sender’s (case) Safety Report Unique Identifier” and “N.2.r.1 Message Identifier”) when submitting the “post-marketing report on adverse drug reaction” and the “clinical trial report on adverse drug reaction”?

A49: [Post-marketing] [Clinical trial]

In this case, a different value shall be used. However, the same value shall be used for “C.1.8.1 Worldwide Unique Case Identification Number.” It is not necessary to enter data on each other C.1.1 in “C.1.9.1.r.2 Case Identifier(s).”

Q50: [Post-marketing] [Clinical trial]

When not all the initials of a patient are known and are not fully entered or are completely omitted, is it allowable to enter “X.X.” in “D.1 Patient (name or initials)”?

A50: [Post-marketing] [Clinical trial]

If the initials of a patient are unknown, not entered etc., nullFlavors shall be used for “D.1 Patient (name or initials).” When the initials are known but are not entered due to protection of personal information, nullFlavors of MSK shall be used.

See Attachments 1 and 2 of Implementation Guide of E2B (R3) and E2B (R3) ICH Q&A for the details on the use of nullFlavors.

Q51: [Post-marketing] [Clinical trial]

Is it necessary to enter all adverse drug reactions and infections reported by the reporters in “E.i Reaction(s)/Event(s) (repeat as necessary)”?

A51: [Post-marketing] [Clinical trial]

All adverse drug reactions and infections reported by the reporters may be entered. Entering only the names of adverse drug reactions and infections subject to reporting based on Articles 228-20 and 273 of the Enforcement Ordinance is also acceptable.

Q52: [Post-marketing] [Clinical trial]

When entering the adverse drug reaction name, is it allowable to enter, for example, only “shock” for a case of “decreased blood pressure, increased heart rate, decreased urinary output, etc.” associated with “shock”?

A52: [Post-marketing] [Clinical trial]

When a reporter determines the case as “shock” based on a re-investigation, etc., it is allowable to enter only “shock” in “E.i Reaction(s)/Event(s) (repeat as necessary).” However, the accompanying symptoms of “decreased blood pressure, increased heart

rate, decreased urinary output, etc.” shall be entered in “H.1 Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information.” See “MedDRA TERM SELECTION: POINTS TO CONSIDER” (PTC) for details on how to enter.

Q53: [Post-marketing] [Clinical trial]

When “E.i.1.1a Reaction / Event as Reported by the Primary Source in Native Language” is entered in Japanese or English, is it permitted not to enter “E.i.1.2 Reaction / Event as Reported by the Primary Source for Translation”?

A53: [Post-marketing] [Clinical trial]

Yes. However, if “E.i.1.1a” is entered in languages other than Japanese or English, “E.i.1.2” shall be entered in Japanese or English.

Q54: [Post-marketing] [Clinical trial]

If a reporter is other than a medical professional (for example, consumer or other non-health professional), is it allowed to interpret “E.i.3.1 Term Highlighted by the Reporter” as “No, not highlighted by the reporter,” or should it be left blank as “unknown”?

A54: [Post-marketing] [Clinical trial]

It shall be entered as determined by the reporter, regardless of his/her qualifications.

Q55: [Post-marketing] [Clinical trial]

How should “E.i.7 Outcome of Reaction / Event at the Time of Last Observation” be entered for the outcomes of adverse drug reactions that did not result in death?

A55: [Post-marketing] [Clinical trial]

An appropriate outcome apart from “death” should be selected for each adverse drug reaction.

Q56: [Post-marketing] [Clinical trial]

When a mother has a miscarriage, which should be entered in “E.i.7 Outcome of Reaction / Event at the Time of Last Observation,” the outcome for the fetus or that of the mother?

A56: [Post-marketing] [Clinical trial]

For the case of fetal death or early miscarriage, the outcome for the parent against the adverse drug reaction name (fetal death, etc.) shall be entered. For example, if the parent recovered, “1 = recovered/resolved” should be entered.

Q57: [Post-marketing]

If there is more than one adverse drug reaction and infection subject to reporting and the suspect drug for each case is different, is it allowable to create more than one report for each suspect drug?

A57: [Post-marketing]

Yes. In that case, the value entered in “C.1.1 Sender’s (case) Safety Report Unique Identifier” of one report shall also be entered in “C.1.10.r Identification Number of the Report Which Is Linked to This Report” of the other report, and vice versa. This should similarly apply to a case where a different adverse drug reaction occurred when more than one dose was administered.

Q58: [Post-marketing]

There are some cases where “G.k.2.1 Medicinal Product Unique Identifier / Pharmaceutical Product Unique Identifier” or other items cannot be specified because “G.k.4.r Dosage and Relevant Information (repeat as necessary),” “G.k.7.r Indication for Use in Case” or other items are unknown. If the sender has received approval for more than one drug product (different brand names), specifications (different contents), formulations (different formulations; routes of administration are the same), and routes of administration with the same active ingredient, which of the drugs is to be reported?

A58: [Post-marketing]

Efforts should be made to specify the drug by conducting an investigation. Even if it is not possible to finally specify the drug, a report should be submitted on the most probable drug determined from the information obtained. When even the most probable drug cannot be determined, it is acceptable to submit a report on the most commonly used drug.

Q59: [Post-marketing]

For a case where the frequency of drug administration is 3 times daily, 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 entered?

A59: [Post-marketing]

For the case of 3 times daily, “8” shall be entered in “G.k.4.r.2” and a UCUM code indicating “hour” in “G.k.4.r.3.” Similarly, for the case of twice daily, “12” and a UCUM code indicating “hour,” respectively, shall be entered; for the case of once every two days, “2” and a UCUM code indicating “day,” respectively; and for the case of once weekly, “1” and a UCUM code indicating “week,” respectively.

Q60: [Post-marketing] [Clinical trial]

Although an adverse drug reaction, etc. occurred during the administration of the suspect drug, the administration continued and the patient recovered from the adverse drug reaction, etc. during the administration period. In this case, how should “G.k.9.i.3.2 Time Interval between Last Dose of Drug and Start of Reaction / Event” be entered?

A60: [Post-marketing] [Clinical trial]

“G.k.9.i.3.2” shall be left blank and “H.1 Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information” shall be entered.

Q61: [Post-marketing]

“Data File on Prescription Drug Name (List of Codes)” (hereinafter referred to as “Code(s) for Re-examination”) is issued based on “Codes of Drugs Listed in Drug Tariff” supervised by the Economic Affairs Division, Health Policy Bureau, MHLW. If a report on adverse drug reactions, etc. is submitted between the approval date for the new drugs, etc. and the time when it is listed in the drug tariff, how should the Code for Re-examination be entered?

A61: [Post-marketing]

Before the “Codes for Re-examination” is issued, the clinical trial drug ingredient code used in the report on adverse drug reactions, etc. in clinical trials shall be entered. In this case, the brand name, generic name, and clinical trial drug ingredient code of the drug shall be registered with the Safety Reports Management Division, Office of Safety I, PMDA.

Q62: [Post-marketing]

Explain how to enter a new drug which has not yet been listed in the “List of Codes of Over-the-counter Drugs” supervised by the Economic Affairs Division, Health Policy Bureau, MHLW.

A62: [Post-marketing]

The reporting company shall promptly register the “Code of Over-the-counter Drug” with the Safety Report Management Division, Office of Safety I, PMDA, after registering it with the Economic Affairs Division. The products of other companies which are not listed in the List of Codes may be entered in Japanese.

Q63: [Post-marketing] [Clinical trial]

Explain what to do for the drugs with characters such as “輸,” “東薬,” “愛薬,” and “阪” in the approval number.

A63: [Post-marketing] [Clinical trial]

The approval number shall be replaced in accordance with the PF/SB/ELD Notification No. 1027-3 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated October 27, 2014, "Handling of Application using Flexible Disks."

Q64: [Clinical trial]

Regarding "case reports on infections in Japan (clinical trial)" and "case reports on adverse drug reactions in Japan (clinical trial)," when an investigational product which has the same active ingredient of the approved drug but has a different formulation and administration route is under development, is it allowable to enter the clinical trial drug ingredient code in "G.k.2.2 Medicinal Product Name as Reported by the Primary Source"?

A64: [Clinical trial]

The clinical trial drug ingredient code shall be entered.

Q65: [Post-marketing]

For overseas cases, which should be entered for the "brand name" in "G.k.2.2 Medicinal Product Name as Reported by the Primary Source," the brand name used in the country in which an adverse drug reaction occurred or that used in Japan?

A65: [Post-marketing]

Overseas brand name shall be entered using single-byte alphanumeric characters, except for own suspect drugs.

In the case of own suspect drugs, the sender shall enter the product code of the products with marketing approval in Japan which he/she considers more appropriate, in consideration of the reason of use, dosage and administration, other active ingredients, etc. of the drug in question.

Q66: [Post-marketing] [Clinical trial]

In the case of fetal death or early miscarriage, which gestation period at fetal death or early miscarriage should be entered, "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"?

A66: [Post-marketing] [Clinical trial]

It should be entered in "H.1."



Q67: [Post-marketing] [Clinical trial]

For the overseas cases, when the comments of the overseas company have already been entered in “H.4 Sender’s Comments” in English, is it allowed to report as written in English?

A67: [Post-marketing] [Clinical trial]

Yes. If the comments of overseas company are entered in languages other than English or Japanese, the comments shall be translated into English or Japanese. Apart from the comments of overseas company, the sender’s comments shall be entered in Japanese.

Q68: [Post-marketing] [Clinical trial]

Implementation Guide of E2B (R3) states that “In the case of multiple sources, the ‘Primary Source for Regulatory Purposes’ is the person who first reported the facts to the sender.” Who is the primary source when the information is obtained via authorities or affiliated companies?

A68: [Post-marketing] [Clinical trial]

The primary source shall be the one which is regarded as the primary source by the authorities or affiliated companies, etc. through which the obtained information passed.

Q69: [Post-marketing] [Clinical trial]

When the CIOMS reporting form or MedWatch reporting form is used for a case report on adverse drug reactions, etc. and all the reported contents are included in the report on adverse drug reactions, etc., is it allowable not to include the form in the “A.1.8.2 List of documents held by sender”?

A69: [Post-marketing] [Clinical trial]

Yes.

Q70: [Post-marketing]

E2B (R3) Three Office Directors’ Notification states that if a report was submitted using the tentative code of an own drug, an additional report shall be immediately submitted when the Code for Re-examination was issued. Is it really necessary to submit an additional report just because the Code for Re-examination was issued?

A70: [Post-marketing]

The additional report shall be submitted for the reports on adverse drug reactions, etc. in Japan only in the case where the Code for Re-examination was issued. For reports on overseas adverse drug reactions, etc., it is sufficient to submit an additional report, when necessary due to other reasons, using the Code for Re-examination after it was issued.

Q71: [Post-marketing] [Clinical trial]

When a case becomes subject to reporting due to an additional report after a withdrawal report, what value should be set for “C.1.8.1 Worldwide Unique Case Identification Number”? Explain how to express that the report is “re-submission after the withdrawal report.”

A71: [Post-marketing] [Clinical trial]

As stated in the Implementation Guide of E2B (R3), when it is required to resubmit a report nullified in the past, a new “C.1.1 Sender’s (case) Safety Report Unique Identifier” and “C.1.8.1” shall be entered, and the reason why the re-submission is required shall be clearly entered in “J2.11 Other References.”

The organization name of the sender who submitted the withdrawal report shall be entered in “C.1.9.1.r.1 Source(s) of the Case Identifier,” and “C.1.1” in “C.1.9.1.r.2 Case Identifier(s).”

## (8) Receipt of Reports

Q72: [Post-marketing] [Clinical trial]

Is it allowed for more than one company in Japan to jointly submit a report on an individual case that occurred overseas? (For example, is it possible to jointly submit a report on an adverse drug reaction caused by a combination drug of Company A and Company B? Or, is it possible to jointly submit a report on the same adverse drug reaction [a case report in overseas literature] from two companies which market or jointly develop a drug with one substance and two names [a jointly developed product]?)

A72: [Post-marketing] [Clinical trial]

Due to the electronic signature system, etc., an electronic report cannot be jointly submitted; each company, therefore, shall submit their own report on adverse drug reactions, etc. Also, CD reports, etc. cannot be jointly submitted; each company, therefore, shall submit their own report on adverse drug reactions, etc. The “C.1.8.1 Worldwide Unique Case Identification Number” should have the same value for each company’s report as far as possible.

Q73: [Post-marketing] [Clinical trial]

A clinical trial was conducted using a drug which Company B has already marketed as a comparator in a double-blind, controlled trial of a new drug (before approval) of Company A, within the scope of the approval. If it is found that an adverse drug reaction was caused by the comparator after unblinding, which should submit the report, Company A or Company B? How should the report be submitted?

A73: [Post-marketing] [Clinical trial]

Company A shall inform Company B of the occurrence of the adverse drug reaction caused by the comparator, and Company B shall submit the “post-marketing report on adverse drug reactions, etc.”

If the “clinical trial report on adverse drug reactions, etc.” has already submitted before unblinding, Company A shall submit the “withdrawal report” stating that the adverse drug reaction was caused by the comparator.

Q74: [Post-marketing] [Clinical trial]

A clinical trial is being conducted for application for partial change of Indications or Dosage and Administration of a drug which has already been marketed in Japan.

- (1) When an adverse drug reaction or infection caused by the test drug occurred in the clinical trial in Japan, which should be submitted, the “post-marketing report on adverse drug reactions, etc.” or “clinical trial report on adverse drug reactions, etc.”?
- (2) Explain how to report when an adverse drug reaction or infection caused by a drug with the same active ingredients as that of the drug concerned occurred overseas.
- (3) Explain how to submit the research reports or foreign corrective action reports.

A74: [Post-marketing]

- (1) It is not necessary to submit the “post-marketing report on adverse drug reactions, etc.” because the provision of Article 228-20 of the Enforcement Ordinance shall not apply to adverse drug reactions and infections caused by a test drug that occurred in a clinical trial conducted in Japan.
- (2) The report shall be submitted based on the provision of Article 228-20 of the Enforcement Ordinance.
- (3) The report shall be submitted based on the provision of Article 228-20 of the Enforcement Ordinance.

[Clinical trial]

- (1) The “clinical trial report on adverse drug reactions, etc.” should be submitted because the provision of Article 273 of the Enforcement Ordinance shall apply to the adverse drug reactions and infections caused by a test drug that occurred in a clinical trial conducted in Japan.
- (2) It is not necessary to submit the report because the provision of Article 273, Paragraph 2 applies to the case.
- (3) The report shall be submitted based on the provision of Article 273 of the Enforcement Ordinance. Furthermore, similar measures in Japan shall be submitted as “foreign corrective action reports on clinical trials,” and the fact that the measures were taken in Japan shall be entered in “J2.11 Other References.”

Q75: [Post-marketing] [Clinical trial]

Explain what to do when new information is obtained after submission of the completion report.

A75: [Post-marketing] [Clinical trial]

If it was judged as a change/addition that affects the evaluation, a completion report shall be newly submitted.

Q76: [Post-marketing]

Regarding the reports on adverse drug reactions, etc. for which the registration number or identification number had already been given on or before October 26, 2003 (i.e., on or before the date when electronic reporting became available), explain how to enter the registration number or identification number when a completion report or additional report is submitted on or after October 27, 2003.

A76: [Post-marketing]

When the first report is submitted on or after October 27, 2003, the case shall be handled as a new case and "J2.1b Identification Number (number)" shall be left blank. The identification number and registration number given on or before October 26, 2003 shall be entered in "C.1.9.1.r.2 Case Identifier(s)" and "J2.11 Other References," respectively. When the identification number is entered in "C.1.9.1.r.2," "true" shall be entered 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."

Q77: [Post-marketing] [Clinical trial]

Regarding the report on the same case, is it allowed to change the reporting method, such as, submitting a paper report as the first report and an electronic report for the second and subsequent reports?

A77: [Post-marketing] [Clinical trial]

The reporting method for subsequent reports on the same case may be changed accordingly.

Q78: [Post-marketing] [Clinical trial]

Is it necessary to replace the identification number when a report additional to the initial report submitted according to E2B (R2) Two Directors' Notification is submitted according to E2B (R3) Two Directors' Notification?

A78: [Post-marketing] [Clinical trial]

The type of report shown in E2B (R3) Two Directors' Notification shall be entered in "J2.1a Identification Number (Type of Report)" and the number given by PMDA at the first report shall be entered in "J2.1b Identification Number (number)."

Q79: [Post-marketing] [Clinical trial]

Is it allowed to submit a report additional to the report which was previously submitted according to E2B (R3) Two Directors' Notification, according to E2B (R2) Two Directors' Notification?

A79: [Post-marketing] [Clinical trial]

Submitting an additional report according to E2B (R2) Two Directors' Notification is not acceptable for a report which was received previously by PMDA according to E2B (R3) Two Directors' Notification. However, this does not apply to the case where a report was submitted according to E2B (R3) Two Directors' Notification but was not accepted.

Q80: [Post-marketing] [Clinical trial]

Regarding an adverse drug reaction, etc. which was reported in "clinical trial report on adverse drug reactions, etc." before the approval date, when additional information was obtained on or after the approval date, which report shall be submitted for the additional information, the "clinical trial report on adverse drug reactions, etc. (additional report)" or "post-marketing report on adverse drug reactions, etc. (the first report)"?

A80: [Post-marketing] [Clinical trial]

An additional report shall be submitted for the adverse drug reactions, etc. which were reported in the "clinical trial report on adverse drug reactions, etc. in Japan" based on the provision of Article 273 of the Enforcement Ordinance. Article 228-20 of the Enforcement Ordinance does not apply to adverse drug reactions, etc. caused by investigational products; therefore, it is not necessary to submit the "post-marketing reports on adverse drug reactions, etc." In this case, "6 = Others" shall be entered in "J2.13.r.3 Development Phase," and characters indicating "after approval" and "brand name" shall be entered in "J2.11 Other References."

Adverse drug reactions, etc. which were reported in the "clinical trial report on adverse drug reactions, etc. overseas," shall be reported as "post-marketing report of adverse drug reactions (the first report)." In this case, the value in "C.1.8.1 Worldwide Unique Case Identification Number" shall be the same as that in "C.1.8.1" of the "clinical trial report on adverse drug reactions, etc. overseas."

Q81: [Post-marketing] [Clinical trial]

Is it necessary to enter "C.1.11 Report Nullification / Amendment" for the report which is in addition to the reports on adverse drug reactions, etc.?

A81: [Post-marketing] [Clinical trial]

Implementation Guide of E2B (R3) states that "C.1.11" shall be used to show the amendment of the report which was previously transmitted. However, in submitting additional reports, it is acceptable if "C.1.11.1 Report Nullification / Amendment" and "C.1.11.2 Reason for Nullification / Amendment" are not always entered.

In submitting reports not subject to reporting, “C.1.11.1” and “C.1.11.2” shall not be entered but “J2.8.1 Flag Meaning Not Requiring Reports” and “J2.8.2 Reasons for Not Requiring Reports” shall be entered.

#### (9) Paper Reports

Q82: [Post-marketing]

When the first report of adverse drug reactions, etc. is submitted by paper report, what are the items to be entered in the attached form of the Secretary-General Notification on Post-marketing?

A82: [Post-marketing]

At least, the items marked with “Ⓢ” (meaning items for which description is mandatory) shown in the Attachments 1 and 2 of E2B (R3) Two Directors’ Notification shall be entered. It is not necessary to describe N items in the report, which are necessary in the case of submitting electronic reports.

Q83: [Post-marketing] [Clinical trial]

Explain how to enter “E.i.3.2 Seriousness Criteria at Event Level” in paper reports.

A83: [Post-marketing] [Clinical trial]

Of the following a to f, what is to be applied shall be entered using alphabetical letters. (more than one choice may be available)

a = Results in Death

b = Is life-threatening

c = Requires inpatient hospitalization or results in prolongation of existing hospitalization

d = Results in persistent or significant disability/incapacity

e = Is a congenital anomaly/birth defect

f = Is a medically important event or reaction

Q84: [Post-marketing] [Clinical trial]

In paper reports, explain how to enter the items other than those listed in “E.i.3.2 Seriousness Criteria at Event Level,” shown in Q83 above, where the allowable values of which are specified as “code value,” “true,” or “false.”

A84: [Post-marketing] [Clinical trial]

It is not mandatory to enter “code value,” “true,” or “false.” Entry should be made so that the content of such items are clear in the report, without referring to the list of codes, etc.

Q85: [Post-marketing] [Clinical trial]

For “D.7.1.r.1a MedDRA Version for Medical History and Concurrent Conditions,” “D.8.r.7a MedDRA Version for Reaction,” or other items, description of the MedDRA

version is required. For paper reports, where should this be entered in the attached form of the Secretary-General Notification on Post-marketing or the Secretary-General Notification on Clinical Trial?

A85: [Post-marketing] [Clinical trial]

It should be entered in the “Comments” column of attached form 1.

Q86: [Post-marketing] [Clinical trial]

Explain how “G.k.9.i.1 Reaction(s) / Event(s) Assessed” should be entered for paper reports.

A86: [Post-marketing] [Clinical trial]

It should be entered so that it can be easily understood which adverse drug reactions/adverse events are being assessed, for example, by adding sequential numbers to the adverse drug reactions/adverse events entered in “E.i Reaction(s) / Event(s).”

#### (10) Electronic Reports

Q87: [Post-marketing] [Clinical trial]

When applying for the connection test to the PMDA’s safety report management system in order to submit reports electronically, when can the connection test be made, i.e., the time and the day of the week?

A87: [Post-marketing] [Clinical trial]

The connection can be tested during PMDA business hours on business days. A detailed schedule will be provided by the Safety Report Management Division, Office of Safety I, PMDA, after an application has been made.

Q88: [Post-marketing] [Clinical trial]

Should the unique number in the file name and the company-unique tracking number entered in “N.1.2 Batch Number” be the same?

A88: [Post-marketing] [Clinical trial]

No, different numbers can be used.

Q89: [Post-marketing] [Clinical trial]

The electronic certificate shall be that of the representative of the company (president and representative director, etc.). Is it allowable to use the electronic signature of the responsible person who was appointed by the president and representative director?

A89: [Post-marketing] [Clinical trial]

No, only the electronic certificate of the representative is acceptable.

Q90: [Post-marketing] [Clinical trial]

Explain what to do in the following case: Unable to submit reports electronically due to suspension of the sender's management system for information on adverse drug reactions. The date on which the system is not available is the end of reporting time frame. Even a paper report cannot be submitted within the time frame because the reporting company is located too far away to submit the report.

A90: [Post-marketing] [Clinical trial]

Call the Safety Report Management Division, Office of Safety I, PMDA to find out what to do.

Q91: [Post-marketing] [Clinical trial]

When "AE," "CA," and an error code are entered in "ACK.A.4," "ACK.B.r.6," and "ACK.B.r.7," respectively, of the acknowledgement messages in ACK files, the report is classified as "the case where additional reports are required." In this case, is this report acceptable?

A91: [Post-marketing] [Clinical trial]

It is acceptable; however, it is to be submitted as an additional report or an amendment report following amendment of the errors.

Q92: [Post-marketing] [Clinical trial]

In the "registration form of the person in charge of reports on adverse drug reactions, etc. (new/change)" for post-marketing and clinical trials, who should be registered (main person and assistants) to be in charge of reports on adverse drug reactions, etc.? Should this be the person in charge of the practical work on reporting or the person in charge of the system related to electronic reporting?

A92: [Post-marketing] [Clinical trial]

Because the registration form of the person in charge of reports on adverse drug reactions, etc. is used to convey instructions regarding re-examination of the submitted reports on adverse drug reactions, etc., revision of Precautions, or submission of the accumulated reported cases of a specific adverse drug reaction, two (main and assistant) persons in charge of the practical work on reporting shall be registered with the Safety Report Management Division, Office of Safety I, PMDA. It is acceptable that the persons in charge of the post-marketing reports and clinical trial reports on adverse drug reactions, etc. are the same persons.

Q93: [Post-marketing] [Clinical trial]

When the same case is transmitted (or submitted) again on the same day, is it necessary to change the file name?



A93: [Post-marketing] [Clinical trial]

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

If PMDA gives instructions, their instructions have priority.

The files shall be transmitted after confirmation of receipt of ACK for the first transmitted report.

Q94: [Post-marketing] [Clinical trial]

Explain the relationship between the expiration date of the electronic certificate and that of public key?

A94: [Post-marketing] [Clinical trial]

The public key will be invalidated after the expiration date of electronic certificate.

Q95: [Post-marketing] [Clinical trial]

What should the file name be when the reporter's public key is stored on CD, etc.?

A95: [Post-marketing] [Clinical trial]

The file should be called "sender ID.cer."

Q96: [Post-marketing] [Clinical trial]

Explain the procedure to be performed when the regulatory authority's public key expires?

A96: [Post-marketing] [Clinical trial]

Approximately one month before the expiration date, PMDA will distribute the new public key to the company submitting the electronic reports. Each company shall switch to the new key when it is received.

Q97: [Post-marketing] [Clinical trial]

Explain what to do in the following case: In-house information system suspended due to natural disaster or other emergencies, or due to critical system failure or other unavoidable reasons (e.g., computer virus infection). The XML file cannot be created before the end of the reporting time frame.

A97: [Post-marketing] [Clinical trial]

Such cases will be handled individually. Contact the Safety Report Management Division, Office of Safety I, and Review Planning Division, Office of Review Management, PMDA for post-marketing and clinical trials, respectively.

Q98: [Post-marketing] [Clinical trial]

The situation in the event of suspension of the management system for information on adverse drug reactions due to natural disaster or other emergencies will be immediately notified to the registered representative's email address for post-

marketing or clinical trials, or on PMDA's website. Explain what to do if companies are also unable to access the Internet and cannot confirm the situation.

A98: [Post-marketing] [Clinical trial]

Call the Safety Report Management Division, Office of Safety I, PMDA to find out what the situation is.

Q99: [Post-marketing] [Clinical trial]

When the parsing check reveals no problems, will all data described in XML be incorporated into the PMDA's safety report management system as the reported information?

A99: [Post-marketing] [Clinical trial]

In the PMDA's safety report management system, only items consistent with XPath stated in the notification are handled as the reported information. Regarding J items, each item shall be created in XML according to XPath as shown in Attachment 4 of E2B (R3) Two Directors' Notification. Regarding the E2B (R3) items, each item shall be created in XML according to XPath as shown in Attachment 3 of the Implementation Guide of E2B (R3).

Q100: [Post-marketing] [Clinical trial]

"F.r.3.3" of the 2.3 ACK.A.5 Other Error List in Attachment 2 of E2B (R3) Three Office Directors' Notification states that the format shall be subject to the standard UCUM format. Show the specific check format.

A100: [Post-marketing] [Clinical trial]

The PMDA's safety report management system checks whether UCUM formats are subject to the syntax rule defined in UCUM. See the following URL for details of the rule and samples of acceptable UCUM codes and other information.

<http://unitsofmeasure.org/trac/>

Q101: [Clinical trial]

When a report is submitted according to E2B (R3) Two Directors' Notification that is additional to the report which was submitted in which "4 = bioequivalence testing," "5 = clinical pharmacology study," or "6 = preparing for application" was entered in "J.12.i.2 Development Phase" according to E2B (R2) Two Directors' Notification, what code shall be entered in "J2.13.r.3 Development Phase"?

A101: [Clinical trial]

The appropriate code shall be entered for cases which fall into the development phase category according to E2B (R3) Two Directors' Notification, otherwise "8 = Others" shall be entered.

## 2. Fax, etc. Reports

Q102: [Post-marketing]

If a “death” suspected of being caused by an adverse drug reaction is revealed through an additional information after submitting an incompleteness report on an adverse drug reaction which cannot be predicted from Precautions, should fax, etc. reports be submitted at the time?

A102: [Post-marketing]

A fax, etc. report shall be immediately submitted. When the fax, etc. report is submitted, the report provided in Article 228-20, Paragraph 1, Item 1 of the Enforcement Ordinance shall be separately submitted.

Q103: [Post-marketing]

If after submitting the fax, etc. report by facsimile, any causal relationship with the suspect drug is ruled out or the fact that the drug was not administered is revealed before submitting the report provided in Article 228-20, Paragraph 1, Item 1 of the Enforcement Ordinance, how should the case be handled?

A103: [Post-marketing]

The Office of Safety II, PMDA should be informed of the situation by facsimile.

Q104: [Post-marketing]

The Secretary-General Notification on Post-marketing states that “cases of death in Japan which are suspected of being caused by an unknown adverse drug reaction shall be immediately reported as the first report by facsimile, etc.” On the other hand, the E2D Guideline states that “An adverse drug reaction associated with a fatal outcome should be classified as an unpredictable adverse drug reaction unless the risk of fatal outcome is clearly described.” Explain when it is necessary to submit a fax, etc. report.

A104: [Post-marketing]

As in the past, a fax, etc. report is required only for a death suspected of being caused by an adverse drug reaction the occurrence of which is unknown. It is not necessary to submit fax reports, etc. on a death suspected of being caused by an adverse drug reaction which is handled as “unknown” based on the E2D Guideline because there is no clear description of the potential for a fatal outcome due to the adverse drug reaction in such items as “Important precautions” and “Clinically significant adverse reactions,” even if it is described in items such as “Clinically significant adverse reactions.”

As in the past, the fax, etc. reports shall be submitted for cases of infections, regardless of whether they are unknown/known.

### 3. Research Reports and Foreign Corrective Action Reports

#### (1) Common Notice of Research Reports and Foreign Corrective Action Reports

Q105: [Post-marketing]

In submitting a research report and foreign corrective action report, when there is more than one product concerned and the report is submitted as a single report, is it acceptable to describe all products concerned using repetition of “G.k Drug(s) Information (repeat as necessary)”?

A105: [Post-marketing]

Yes.

Q106: [Post-marketing] [Clinical trial]

In submitting a research report or foreign corrective action report, is it necessary to submit all data owned by the reporting company?

A106: [Post-marketing] [Clinical trial]

It is not necessary to submit all the owned data. However, the literature concerned, CCDS, etc. shall be submitted, regardless of whether they were published or not.

#### (2) Research Reports

Q107: [Post-marketing]

What is being referred to by a research report demonstrating “that there is a risk of occurrence of cancers or other serious diseases, disabilities, or death due to an adverse drug reaction caused by the drug or overseas drug or due to infections caused by their use” in the Secretary-General Notification on Post-marketing?

A107: [Post-marketing]

It means, for example, those research reports demonstrating that there is a risk of occurrence of death or disabilities such as cancer, deafness, and blindness caused by the ingredients contained in the drug.

The research reports referred to mean those published in academic journals, etc. in Japan or overseas, or reports made in-house or at affiliated companies, regardless of whether they are published or not. Specifically, they include reports on epidemiologic studies (or summary/analysis of adverse drug reactions), study results using animals, etc., and results of physical or chemical tests.

Q108: [Post-marketing] [Clinical trial]

When “a research report demonstrating that there is no efficacy for the approved Indications” (for clinical trials, “a research report demonstrating that there is no efficacy for the approved Indications for diseases subject to the clinical trials”) is submitted, which report should be submitted, “a research report on infections” or “a research report on adverse drug reactions”?

A108: [Post-marketing] [Clinical trial]

“Research report on adverse drug reactions” shall be submitted.

Q109: [Post-marketing] [Clinical trial]

When the results of animal studies are submitted as the research report, what should be selected for “C.1.3 Type of Report”?

A109: [Post-marketing] [Clinical trial]

“2 = Report from study” shall be selected.

Q110: [Post-marketing] [Clinical trial]

Of the published documents, which should be submitted as the case report, the case report on adverse drug reactions or infections, or the research report?

A110: [Post-marketing] [Clinical trial]

A case report describing information shown in 3.3.1 Minimally required information of Attachment 1 of Implementation Guide of E2B (R3) shall be submitted as the case report on adverse drug reactions or infections.

However, published documents including information demonstrating a significant change in the incidence trends of an adverse drug reaction or infection, or no efficacy or effect that was approved for the drug shall also be submitted as a research report.

### (3) Foreign Corrective Action Reports

Q111: [Post-marketing]

Regarding the corrective actions taken overseas, explain what actions among the following fall under the category of “cessation of manufacturing, import or marketing, recalls, disposal, and other actions to prevent the occurrence or expansion of hygienic hazards.”

- (1) Change of Indications, Dosage and Administration
- (2) Cessation of manufacturing, import, and marketing
- (3) Recalls and disposal of the products
- (4) Revision of Precautions
- (5) Discontinuation of clinical trials

A111: [Post-marketing]

The following cases fall into the category of foreign corrective action:

- (1) Cases where limitation of Indications and Dosage and Administration are implemented because of issues of efficacy or safety. Expansion of Indications or Dosage and Administration do not need to.
- (2) Cases where the cessation of manufacturing, import, or marketing, and change of manufacturing method, etc. are implemented because of issues of efficacy or safety. (For example, introduction of inactivation process to prevent viral contamination of blood products.) The cessation of manufacturing, import, or

marketing, and change of manufacturing method, etc. solely for business reasons do not need to be reported.

- (3) Cases where recalls or disposal is conducted because of issues of efficacy or safety, including spontaneous recalls. Recalls and/or disposal solely for business reasons do not need to be reported.
- (4) Cases of the revision of Precautions which includes important changes, etc.
- (5) Cases of discontinuation of all clinical trials because of issues of safety.

Q112: [Clinical trial]

Regarding foreign corrective action, what examples are included in “cessation of manufacturing, import or marketing, recalls, disposal, and other actions to prevent occurrence or expansion of hygienic hazards”?

A112: [Clinical trial]

The following cases fall under the category of foreign corrective action:

- (1) Change or limitation of Indications or Dosage and Administration because of issues of efficacy or safety;
- (2) Cessation of manufacturing, import, or marketing, and change of manufacturing method, etc. because of deficiency in efficacy or issues of safety. (For example, introduction of inactivation process to prevent viral contamination of blood products.)
- (3) Recalls or disposal because of issues of efficacy or safety (including spontaneous recalls)
- (4) Revision of Precautions which includes important changes, etc.
- (5) Discontinuation or termination of all clinical trials because of issues of efficacy, safety, or quality.
- (6) Strengthening, etc. of safety measures by distribution of doctor letters, etc. during clinical trials

Q113: [Post-marketing] [Clinical trial]

When information related to efficacy, safety, proper use, etc. was provided from the regulatory authorities overseas, etc., for example, information that is necessary to prevent or reduce serious adverse drug reactions, adverse events, medical accidents, etc., regardless of predictability from Precautions or the investigator’s brochure, etc., should this be submitted as a foreign corrective action report?

Explain the specific cases.

A113: [Post-marketing] [Clinical trial]

It is to be reported.

Revision of Precautions, information on recalls, etc. may be considered as information provided from regulatory authorities overseas.

The foreign corrective action reports include the cases where precautions on serious adverse drug reactions are additionally entered in “BOXED WARNING” of the US

package insert. Furthermore, when information on revision of Precautions is obtained, whether it falls under the category of a foreign corrective action report shall be determined based on an appropriate evaluation as to whether or not it is “information that is necessary to prevent or reduce serious adverse drug reactions, adverse events, medical accidents, etc.”

Regulatory authorities overseas are not limited to those in the USA shown above, EU, and UK. Information on foreign corrective action obtained from affiliated companies overseas shall be handled similarly as mentioned above.

#### 4. Periodic Report on Unknown/Nonserious Adverse Drug Reactions

##### (1) Reporting Method

Q114: [Post-marketing]

Regarding “other drugs” not subject to periodic safety reporting, is it allowed to submit a single periodic report on unknown/nonserious adverse drug reactions for the same active ingredient with different routes of administration?

A114: [Post-marketing]

Separate reports are to be submitted for drugs with different routes of administration, even if they have the same active ingredient. However, it is allowed to submit a single report for drugs with the same package insert.

Q115: [Post-marketing]

Regarding a product with more than one approval date, etc. because of additional indications, different content, etc., is it allowed to submit a single, summarized periodic report on unknown/nonserious adverse drug reactions?

A115: [Post-marketing]

Yes. In that case, the initial date of reporting obligation for reporting shall be the approval date among those for products with different indications or contents which leads to the earliest date of submission on and after April 1, 2005.

Q116: [Post-marketing]

Regarding over-the-counter drugs containing the same ingredients but in different amounts, is it allowed to submit a single, summarized periodic report on unknown/nonserious adverse drug reactions?

A116: [Post-marketing]

A single, summarized report may be submitted for the products containing the same ingredients.

Q117: [Post-marketing]

Regarding over-the-counter drugs including cold medicines, antipyretic analgesic, etc. containing a slightly different ingredient among the active ingredients, is it allowed to submit a single, summarized periodic report on unknown/nonserious adverse drug reactions?

A117: [Post-marketing]

When the product is a drug, etc. such as a cold medicine, antipyretic analgesic, etc. for which approval standards for manufacturing (import) have been established, contains the same type, etc. of major active ingredients, and it is judged by the company to be appropriate to take safety measures such as revision of Precautions at the same time, it is allowed to submit a single, summarized report.

In this case, the reason why the single, summarized report was submitted shall be provided in the "Comments" column of Part 7 of the attached form of the Secretary-General Notification on Post-marketing.

Q118: [Post-marketing]

When a single, summarized report of drugs with different strength or formulation, etc. is submitted, is it allowed to enter the names of drugs which do not cause unknown/nonserious adverse drug reactions in the column of "brand name," etc.?

A118: [Post-marketing]

The names of drugs which do not cause unknown/nonserious adverse drug reactions shall not be entered. Only the name of the drugs which caused unknown/nonserious adverse drug reactions shall be entered.

Q119: [Post-marketing]

For jointly developed products, is it allowed to jointly prepare and submit the periodic report on unknown/nonserious adverse drug reactions even after the end of re-examination period?

A119: [Post-marketing]

This is permitted.

Q120: [Post-marketing]

When an adverse drug reaction caused by a drug with unknown specification is collected, for the brand name column of Part 7 of the attached form, should it be left blank or described as an unknown specification?

A120: [Post-marketing]

All suspect brand names shall be entered in Part 7 of the attached form. "Unknown brand name" shall be entered in the comments column for the case in the list.



## (2) Initial Date of Reporting Obligation

Q121: [Post-marketing]

After submitting the periodic safety report for a drug subject to periodic safety reporting, is it allowed to change the initial date of reporting obligation to the international birthdate or approval date of the drug, etc.?

A121: [Post-marketing]

Such changes are acceptable. However, the reporting interval of the first report after the change shall not exceed 1 year.

For example, when the initial date is changed from June 30 to September 30, the first report shall be submitted within the reporting interval of June 30 to September 29; the subsequent reports shall use the initial date of September 30 for reporting.

When there was no information on adverse drug reactions to be reported during the first reporting period after the change and the periodic report on unknown/nonserious adverse drug reactions was not submitted, the fact that there was no information on adverse drug reactions to be reported during the previous reporting interval shall be entered in the comments column of the next report.

Q122: [Post-marketing]

Regarding a product which has the same active ingredient as the specified drug subject to periodic safety reporting and for which it is appropriate to take safety measures at the same time, is it allowed to make the initial date of reporting obligation for the periodic report on unknown/nonserious adverse drug reactions of the product the same date as the drug subject to periodic safety reporting?

A122: [Post-marketing]

It is acceptable. However, the reporting interval shall not exceed 6 months if the initial date of reporting obligation is within 2 years after approval. It shall not exceed 1 year if the initial date of reporting obligation is more than 2 years after the approval.

Q123: [Post-marketing]

When the reporting interval of the periodic safety report is shortened according to Part 5 (4) of PFSSB Notification No. 0517-2 issued by the Secretary-General of the Pharmaceutical and Food Safety Bureau, MHLW, dated May 17, 2013, "Enforcement of the Ministerial Ordinance to Partially Revise the Ordinance for Enforcement of the Pharmaceutical Affairs Act and Periodic Safety Report System on New Prescription Drugs," is it allowed to set the reporting interval of the periodic report on unknown/nonserious adverse drug reactions so that it coincides with that of the periodic safety report?

A123: [Post-marketing]

It is acceptable.

Q124: [Post-marketing]

Regarding “Other drugs” that are not subject to periodic safety reporting, what does “international birthdate or approval date of the drug, etc.,” which may be the initial date of reporting obligation, specifically indicate?

A124: [Post-marketing]

It indicates:

- International birthdate
- Approval date
- Initial date of reporting obligation of the periodic safety report (available even after the end of re-examination period)
- Date designated by the marketing authorization holder for submitting CD reports, etc.

Q125: [Post-marketing]

Regarding “Other drugs” that are not subject to periodic safety reporting, the initial date of reporting obligation shall be the international birthdate or approval date of the drug, etc. Is it possible to change the initial date of reporting obligation in the case where this is deemed necessary from the viewpoint of safety measures?

A125: [Post-marketing]

Such cases need to be individually determined in consultation with Office of Safety II, PMDA.

Q126: [Post-marketing]

A report was submitted for a drug included in “Other drugs” not subject to periodic safety reporting using the approval date of the drug as the initial date of reporting obligation; however, a new initial date of reporting obligation of the periodic safety report will be required because of the additional Indications, etc. Explain how to deal with this situation.

A126: [Post-marketing]

The initial date of reporting obligation shall be changed to the date designated by the Minister of Health, Labour and Welfare, associated with the periodic safety report. In this case, the reporting interval of the first report after the change shall not exceed 1 year.

For example, when the initial date is changed from June 30 to September 30, the first report shall be submitted within the reporting interval of June 30 to September 29; the subsequent reports shall use the initial date of September 30 for reporting.

When there was no information on adverse drug reactions to be reported during the first reporting period after the change and the periodic report on unknown/nonserious adverse drug reactions was not submitted, the fact that there was no information on adverse drug reactions to be reported during the previous reporting interval shall be entered in the comments column of the next report.

Q127: [Post-marketing]

A new approval date and approval number are given when the application for approval of a new substitute is filed as a measure to prevent medical accidents, etc. In this case, on what date should reporting commence?

A127: [Post-marketing]

When the approval date is set as the initial date of reporting obligation, either the former or new approval date may be the initial date.

When a report is submitted using the former approval date as the initial date, the following shall be entered in the comments column: new approval date and approval number, and the fact that a new substitute was approved during the reporting interval.

Furthermore, when a report is submitted using the new approval date as the initial date of reporting obligation, a report based on the former approval shall be submitted no later than the day prior to the approval date for the new substitute, and the fact that the report is submitted within a period of less than 1 year due to the application for the new substitute shall be entered in the comments column. The following reports shall be submitted using the new approval date as the initial date. If there was no information on adverse drug reactions to be reported during the first reporting period after the initial date was changed and a periodic report of unknown/nonserious adverse drug reactions was not submitted, the fact that there was no information on adverse drug reactions to be reported during the previous reporting interval shall be entered in the next report. If information on adverse drug reactions caused by the products with the former approval is obtained on and after the date of new approval, the report shall be submitted regarding it as information on the new approval.

Q128: [Post-marketing]

The periodic report on unknown/serious adverse drug reactions for drugs subject to periodic safety reporting shall be submitted within 70 days after the termination date of the investigation period. What day should the termination date of the investigation period be?

A128: [Post-marketing]

The reporting time frame shall be set using the termination date of the investigation period (the end day of investigation period) as Day 0.

If the end date of the reporting time frame does not fall on a PMDA business day, the date shall be the following business day.

### (3) Adverse Drug Reactions Subject to Reporting

Q129: [Post-marketing]

Explain how to handle in the following cases:

- (1) in the case where an adverse drug reaction that was submitted in the individual case safety report becomes subject to periodic reporting on unknown/nonserious adverse drug reactions because of additional information.
- (2) in the case where an adverse drug reaction that was subject to periodic reporting on unknown/nonserious adverse drug reactions becomes excluded from those subject to the report because of additional information.
- (3) in the case where an adverse drug reaction that was subject to periodic reporting on unknown/nonserious adverse drug reactions becomes subject to individual case safety reporting because of additional information.
- (4) in the case where an adverse drug reaction that was submitted in the periodic report on unknown/nonserious adverse drug reactions becomes excluded from those subject to reporting because of additional information.
- (5) in the case where an adverse drug reaction that was submitted in the periodic report on unknown/nonserious adverse drug reactions becomes subject to individual case safety reporting because of additional information.

A129: [Post-marketing]

- (1) It shall be submitted as the periodic report on unknown/nonserious adverse drug reactions.  
The individual case safety report shall be submitted not as the withdrawal report but as a report not subject to reporting based on the reporting criteria. See Attachment 2 of E2B (R3) Three Office Directors' Notification for specific descriptions.
- (2) It is acceptable not to submit the periodic report on unknown/nonserious adverse drug reactions.
- (3) The individual case safety report shall be submitted within the reporting time frame using the date when information by which the case can be determined to be subject to individual case safety reporting was obtained as the initial date. In this case, the history shall be clearly described in "J2.2.2 Comments on Initial Date for Reporting."
- (4) It is not necessary to submit the withdrawal or replacement report of the periodic report on unknown/nonserious adverse drug reactions.
- (5) The individual case safety report shall be submitted within the reporting time frame using the date when information by which the case can be determined to be subject to individual case safety reporting was obtained as the initial date. In this case, the history shall be clearly described in "J2.2.2 Comments on Initial Date for Reporting."

Q130: [Post-marketing]

Explain how to handle in the following cases:

- (1) A case was submitted in the periodic report on unknown/nonserious adverse drug reactions during the reporting interval; however, any relationship was ruled

out during the next reporting interval. In this case, is it necessary to describe this in the next report?

- (2) A case was submitted in the periodic report on unknown/nonserious adverse drug reactions during the reporting interval and remained unknown/nonserious in the next reporting interval. When additional information is obtained during the next reporting interval, should a periodic report again be submitted on unknown/nonserious adverse drug reactions?
- (3) Regarding a case submitted in the periodic report on unknown/nonserious adverse drug reactions during the reporting interval, additional information revealed the occurrence of a new unknown/nonserious adverse drug reaction. In this case, should the periodic report be submitted on unknown/nonserious adverse drug reactions?

A130: [Post-marketing]

The cases above shall be handled as follows:

- (1) It is not necessary to describe this.
- (2) It does not need to be reported unless there is a change in the seriousness determination.
- (3) The new, unknown/nonserious adverse drug reaction is to be reported.

Q131: [Post-marketing]

Unknown/serious and unknown/nonserious adverse drug reactions occurred and the individual case safety report on an unknown/serious adverse drug reaction was submitted including the name of unknown/nonserious adverse drug reaction. In this case, is it necessary to submit the periodic report on unknown/nonserious adverse drug reactions separately?

A131: [Post-marketing]

It is necessary.

Q132: [Post-marketing]

Explain how to handle in the following cases:

- (1) the case where the nonproprietary name was identified but the brand name was not identified;
- (2) the case where the marketing authorization holder and the brand name of the product was identified but the route of administration was not identified.

A132: [Post-marketing]

The report shall be submitted for the cases as follows:

- (1) The case shall be handled as an own product and a periodic report on unknown/nonserious adverse drug reactions shall be submitted.
- (2) The report shall be submitted on the product with the most probable route of administration.

Q133: [Post-marketing]

Regarding a slight adverse drug reaction that cannot be predicted from Precautions, which is not subject to reporting based on the reporting criteria in the Former Reporting Standard, additional information was obtained on and after April, 1, 2005, but there was no special change in the assessment. In this case, is it necessary to submit a periodic report on unknown/nonserious adverse drug reactions of the drug concerned?

A133: [Post-marketing]

Reporting is not necessary.

#### 5. Handling of cases which are directly reported to the authorities

Q134: [Post-marketing]

Regarding cases where information on adverse drug reactions, etc. which the marketing authorization holder obtained from PMDA, is it necessary for the marketing authorization holder to newly submit a report on adverse drug reactions, etc. to PMDA?

A134: [Post-marketing]

In principle, it is not necessary for the marketing authorization holders to submit a report on adverse drug reactions, etc. for cases where information on adverse drug reactions, etc. is provided by PMDA. However, a report on adverse drug reactions, etc. shall be submitted in the following cases:

- (i) when the information provided by PMDA is on a case for which PMDA has not conducted a detailed investigation and which falls under the category of Article 228-20 of the Enforcement Ordinance;
- (ii) when information (regardless of its volume) on the same case was obtained from medical institutions other than PMDA, literature, etc. and where the case falls under the category of Article 228-20 of the Enforcement Ordinance even if a detailed investigation has been conducted by PMDA.

Q135: [Post-marketing]

A case for which a detailed investigation was conducted by PMDA may be used when taking safety measures. Explain what to do when it is desirable to release such a case as the evidential case in notification of the revised package insert.

A135: [Post-marketing]

Contact the Safety Report Management Division, Office of Safety I, PMDA in advance to release the case.

Q136: [Post-marketing]

Regarding case information obtained from adverse drug reaction reports from patients and which has been released by PMDA, is it necessary for the marketing authorization holders to submit a new report on adverse drug reactions, etc. to PMDA?

A136: [Post-marketing]

The marketing authorization holders shall, regardless of whether PMDA releases such information or not, submit a report on adverse drug reactions, etc. when information (regardless of its volume) on the same case is obtained from medical institutions, literature, etc. other than the report on adverse drug reactions from patients released by PMDA for the cases listed in the provision of Article 228-20 of the Enforcement Ordinance.

If the information gathered by the marketing authorization holders includes no further information than already released information, it is not necessary to submit a new report on adverse drug reactions, etc.