

## Description of J Data Elements and E2B Data Elements

### 1. Entry of dates (common to J data elements and E2B data elements)

- When entering dates, use the Western calendar for the year.
- When entering the information that does not fit the data type such as “around 5:00 p.m. on September 1, 2020” to the element with the data type of “CCYYMMDDHHMMSS.UUUU[+|-ZZzz],” enter up to “20200901,” which fits the data type, in this element and enter “around 5:00 p.m.” in the element the sender considers to be most suitable for entering the information concerned.
- Use Japan Standard Time when entering all the elements related to dates and time for cases in Japan, and at least the elements related to dates and time shown in the table below for overseas cases. The time difference [+|-ZZzz] from the Coordinate Universal Time (UTC) does not need to be entered.

For overseas cases, Japan Standard Time does not have to be used for the elements related to dates and time other than those shown in the table below, but relative temporal relations between elements should be maintained. The accuracy of the required date and time is specified for each element. For details, refer to the E2B (R3) Implementation Guide Notification and the 2020 E2B (R3) Two Director Notification.

Elements for which Japan Standard Time is used for overseas reports	
J2.2.1	Base Date for Reporting
N.1.5	Date of Batch Transmission
N.2.r.4	Date of Message Creation
C.1.2	Date of Creation
C.1.4	Date Report was First Received from Source
C.1.5	Date of Most Recent Information for This Report

### 2. Description in individual case safety reports

#### (1) Post-marketing (excluding reports of adverse reactions to quasi-drugs, etc.)

##### A. J data elements

##### (a) Identification Number (reporting category) (J2.1a)

When “Report Nullification / Amendment (C.1.11.1)” is reported as “2 = Amendment,” the report shall be regarded as an additional report. Therefore, as is the case with a usual additional report, the same reporting category as the previous report should be entered for reporting.

##### (b) Comment on Base Date for Reporting (J2.2.2)

Describe it in the following manner.

- When the “Date Report Was First Received from Source (C.1.4)” and the “Base Date for Reporting (J2.2.1)” are different for the first report.

Example)

- If a report is submitted again for the same case after the withdrawal report, summarize the background.
  - If the case was originally not considered to be subject to an individual case safety report, but is found to be subject to an individual case safety report based on additional information, summarize the background.
  - If an additional report of an individual case safety report (clinical trial) is made on or after the approval date as an individual case safety report (post-marketing), state this.
  - If the sender is aware of the fact that the reporting deadline specified in Article 228-20, Paragraph 1, Items 1 and 2 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ministry of Health and Welfare Ordinance No. 1 of 1961; hereinafter referred to as the “Regulation”) has passed, state this.
  - If the case was originally considered to be subject to reporting within 30 days, but is found before the initial report to be subject to reporting within 15 days based on the additional information, summarize the background.
- (c) Status Category of New Drugs, etc. (J2.4.k)
- Regardless of the approval application category, cases obtained during the early post-marketing phase vigilance must be reported as those under early post-marketing phase vigilance. For a drug that has been approved based on the application for partial change in approved product information, if the change is subject to the early post-marketing phase vigilance and if the use of the drug falls into the category of changes subject to the early post-marketing phase vigilance or if it is unknown whether or not it falls into this category, the case shall be reported as the one under the early post-marketing phase vigilance. If the use of the drug does not fall into the category of changes subject to early post-marketing phase vigilance, the case shall be reported according to the status classification based on the approval as a drug with a new active ingredient.
  - Even for drugs that have been approved within the past 2 years, the report should be made entering “not applicable” if Article 228-20, Paragraph 1, Item 1 (d) of Regulation is not met and the case is not one that has been obtained from the early post-marketing phase vigilance.
  - For a generic drug, “not applicable” should be entered even if it has been approved within the past 2 years.
  - For a follow-on biologic, the status category shall be described according to the status category based on the first approval as a follow-on biologic.
  - In this element, the category of the sender’s in-house suspected drug at the time of reporting shall be entered. Therefore, the category may be changed in an additional report.
- (d) Future Actions (J2.10)

When entering this element for an overseas case, enter the action of the sender, not the action of the overseas company.

If the sender considers it necessary to revise PRECAUTIONS, etc., the sender should consult the Office of Pharmacovigilance I or the Office of Pharmacovigilance II, PMDA (the Office of Manufacturing Quality and Vigilance for Medical Devices in the case of in vitro diagnostics), separately.

(e) Other Reference Matters, etc. (J2.11)

Describe other reference matters.

○ Status of description, etc. of PRECAUTIONS

If the reporting deadline is in 15 days or if the reporting deadline is in 30 days and the event is determined as the known fact based on the description in “Other adverse reactions,” the description status shall be described.

○ Cases covered by the Relief System for Sufferers from Adverse Drug Reactions or cases covered by the Relief System for Infections Acquired through Biological Products

When reporting cases for which information has been provided by PMDA to a company, the fact that they are “cases covered by the relief systems for sufferers of adverse reactions/infection,” the date of issuance of the payment determination notification, the issuance number of the payment determination notification, the reference number, and the date of payment determination shall be entered. If two reference numbers are given for the same case according to the type of benefit, only one reference number may be entered.

○ Information on blinded comparator

Regarding reports from blinded clinical studies, etc. conducted after marketing using an approved in-house drug, if the study has not been unblinded, information such as the generic name and dose of the comparator, etc. shall be reported. For overseas cases, it is acceptable to provide information such as generic name, dose, etc. of the comparator, etc. to the extent possible.

B. E2B data elements

(a) Identification information (C data elements)

○ Does This Case Fulfil the Local Criteria for an Expedited Report? (C.1.7)  
“false” must be selected to the report as a case not subject to reporting.

○ Worldwide Unique Case Identification Number (C.1.8.1)

- Regarding the reports of adverse reactions, etc. from medical institutions, when a company reports a PMDA-investigated case for which an ICSR file was received, enter the identifier given by PMDA in this element.
- When a case reported as a report of adverse reactions, etc. in clinical trials after the date of approval is switched to a post-marketing report of adverse reactions, etc., the identifier entered in the report of adverse reactions, etc. in clinical trials shall be entered in this element.

○ Source(s) of the Case Identifier(s) (C.1.9.1.r)

Regarding reports of adverse reactions, etc. from medical institutions, if the PMDA provides information and a company makes a report based on the information, “pmda” shall be entered in the “Source(s) of the Case Identifier (C.1.9.1.r.1),” and the medical institution report number entered in the drug safety report shall be entered in “Case Identifier(s) (C.1.9.1.r.2).” If there are multiple drug safety reports, this element shall be repeated to enter all medical institution report numbers.

○ Report Nullification / Amendment (C.1.11.1)

When this element is reported as “2 = Amendment,” the report will be regarded as an additional report, and therefore, it shall be handled as is the case with a usual additional report.

- Type of Report (C.1.3), Qualification (C.2.r.4), and Study Identification (C.5)
  - When reporting cases reported from use-results surveys, specified use-results surveys, or post-marketing clinical studies, etc., enter “2 = Report from study” in Type of Report (C.1.3) and enter the information on the survey or study concerned in Study Identification (C.5).
  - Regarding the reports of adverse reactions, etc. from medical institutions, when a company reports a case of information provided by PMDA, describe “Type of Report (C.1.3)” according to the information obtained in the investigation conducted by the sender. However, if the information on the report type is not obtained as a result of the investigation, “4 = Not available to sender (unknown)” may be entered. “Qualification (C.2.r.4)” shall be entered according to the qualification of the primary information source.
- (b) Patient Characteristics (D data elements)
  - Patient (D.1)
 

Enter initials in Roman characters (half-width). In principle, a period (half-width, “.”) shall be placed after each Roman character. For overseas cases, it is basically acceptable to use the sent initials as they are.
  - Reported Cause(s) of Death (free text) (D.9.2.r.2)
 

Describe in Japanese for cases in Japan and in Japanese or English for overseas cases.
- (c) Reaction(s) / Event(s) (E data elements)
  - Reaction / Event as Reported by the Primary Source in Native Language (E.i.1.1a)
 

When the name of the adverse reaction reported by the primary information source is different from the MedDRA term entered in “Reaction / Event (MedDRA code) (E.i.2.1b),” this element needs to be entered.
- (d) Drug(s) Information (G data elements)
  - If information on health food, etc. is available, it should not be described in Drug(s) Information (G data elements), but described in Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information (H.1).
  - When reporting in a blinded manner, enter “true” in “Investigational Product Blinded (G.k.2.5),” and information on the study drug in the elements included in “Drug(s) Information (G.k).” In addition, enter the information such as the generic name, dose, etc. of the comparator, etc. in “Other Reference Matters, etc. (J2.11).”
  - Characterisation of Drug Role (G.k.1)
 

Enter information for all drugs described. If suspected drugs are different for multiple adverse reactions, etc., select “1” (= Suspect) or “3” (= Interacting) for all the suspected drugs for each adverse reaction, etc.
  - Medicinal Product Name as Reported by the Primary Source (G.k.2.2)
    - [1] In-house products
      - For prescription drugs (excluding in vitro diagnostics), enter the 9-digit re-examination code using the “Prescription drug data file (code table)” (hereinafter referred to as the “re-examination code”). For drugs such as generic drugs, for which no 9-digit re-examination code has been given, but a 7-digit re-examination code is known, be sure to enter the 7-digit re-examination code

in this element in addition to “Substance / Specified Substance Name (G.k.2.3.r.1).” Enter a provisional code until a re-examination code is given after approval.

- For drugs requiring guidance or over-the-counter drugs, enter the applicable code using the “Drug brand code” (12 digits). If the product name of the suspected drug cannot be identified, enter the code of the most suspected drug and report to that effect in “Other Reference Matters, etc. (J2.11).” For drugs requiring guidance or over-the-counter drugs for which drug brand code has not been obtained, register and enter the provisional code.
- For in vitro diagnostics or pharmacy-made pharmaceuticals, enter the code for reporting adverse reactions, etc.
- Enter a provisional code when reporting a test drug as a suspected concomitant drug.

[2] Products of other companies

- For suspected drugs of other companies, enter a 9-digit or 7-digit (for prescription drugs [excluding in vitro diagnostics]) or 12-digit (for drugs requiring guidance or over-the-counter drugs) code using the re-examination code whenever possible. If there is no 9-digit re-examination code or 9-digit re-examination code is unknown, but a 7-digit re-examination code is known, be sure to enter the 7-digit re-examination code in this element in addition to entering it in “Substance / Specified Substance Name (G.k.2.3.r.1).” If the code is unknown, enter the brand name. If neither is known, available information such as the generic name may be provided in Japanese. For overseas cases, it is acceptable to enter an English name.
- If the code and drug name are unknown and the only available information is the number, etc. of suspected drugs or concomitant drugs, repeat G.k.2.2 as many times as the number of drugs and enter “UNKNOWNDRUG.” Although it is preferable to provide other available information for each drug, if any, it is acceptable to provide obtained information in “J2.11 Other Reference Matters, etc.”

○ Substance / Specified Substance Name (G.k.2.3.r.1)

[1] In-house products

- For prescription drugs (excluding in vitro diagnostics), use the re-examination code (7 digits). For prescription drugs for which no code has been obtained, enter the provisional code.
- For drugs requiring guidance or over-the-counter drugs, if there is an applicable re-examination code (7 digits) for active ingredients, enter this code. If there is no re-examination code, enter the name of active ingredients.
- For in vitro diagnostics or pharmacy-made pharmaceuticals, enter the code for reporting adverse reactions, etc.
- Enter a provisional code when reporting a test drug as a suspected concomitant drug.

[2] Products of other companies

- For suspected drugs of other companies, enter a 7-digit (for prescription drugs [excluding in vitro diagnostics]) or 12-digit (for drugs requiring guidance or over-the-counter drugs) code using the re-examination code whenever possible. If the code is unknown, enter the generic name (brand name for drugs requiring

guidance or over-the-counter drugs). If the generic name is also unknown, enter the therapeutic category number (3-digit code). If neither is known, available information may be provided in Japanese. For overseas cases, it is acceptable to enter an English name.

- Common precautions for Medicinal Product Name as Reported by the Primary Source (G.k.2.2) and Substance / Specified Substance Name (G.k.2.3.r.1)
  - For in-house products, if a code exists, the code should be used for all entries.
  - Enter the code in half-width characters.
  - For overseas cases, if any drug with the same route of administration has been approved in Japan, the code of this drug should be entered, in principle. If no drug with the same route of administration has been approved in Japan, the code of the drug with the route of administration that is judged most relevant as information among the drugs with different routes of administration approved in Japan should be entered.
  - See 8. of Attachment 9 for registration of provisional codes or issuance of codes for reporting of adverse reactions, etc.
  - If a report of adverse reactions, etc. in Japan is made using a provisional code for an in-house product, an additional report shall be made promptly when a code is given. As a rule, reports are received from the day after the re-examination code is given. For drug brand codes, if a receipt error occurs, contact the Safety Report Management Division, Office of Informatics and Management for Safety, PMDA.
- Investigational Product Blinded (G.k.2.5)

This element should be “true” if the suspected drug is blinded, and if the event turns out to have been caused by the test drug after unblinding, delete the entry in this element and make an additional report.
- Dose (G.k.4.r.1)

Enter the dose per administration. If the dose per administration is unknown but the daily dose is known, enter the daily dose in this element and 1 day in Definition of the Time Interval Unit (G.k.4.r.3).
- Duration of Drug Administration (number) (G.k.4.r.6a)

When entering the number of days, the start date of administration should be considered as “1” to count the days.
- Pharmaceutical Dose Form (free text) (G.k.4.r.9.1)

This element should be entered in half-width alphabet characters according to Appendix 7, “List of Dosage Forms,” of 2020 E2B (R3) Two Director Notification.
- Route of Administration TermID (G.k.4.r.10.2b)/Parent Route of Administration TermID (G.k.4.r.11.2b)

These elements shall be described in half-width numeric characters according to the ICH E2B code list in Appendix I (F) of Attachment 1 of E2B (R3) Implementation Guide Notification. If there is no appropriate route of administration in the code list, select “050 = Other.” “Route of Administration (free text) (G.k.4.r.10.1)” or “Parent Route of Administration (free text) (G.k.4.r.11.1)” should be described in Japanese for the cases in Japan, and in Japanese or English for the overseas cases.
- Assessment of Relatedness of Drug to Reaction(s) / Event(s) (G.k.9.i.2.r)

At least for in-house suspected drugs, the relationship with all adverse reactions,

etc. stated in the report should be described.

○ Additional Information on Drug (G.k.11)

If a separate malfunction report for the machine/equipment part has been submitted using Attached Form 8 of the Post-marketing Director-General Notification for the adverse reaction report of the drug part of a combination product, enter “\$COMBI\$” in this element using half-width symbols and half-width alphabet capital letters to indicate that the case is identical.

The string of characters to be entered if the “unique safety report identifier” cannot be entered, which is shown in 3. (2) A (g) in Attachment 1 of “Points to Consider for Reports of Medical Device Malfunctions, etc.” (PMDA/OMQVMD Notification No. 0131001 of the Office of Manufacturing Quality and Vigilance for Medical Devices, Pharmaceuticals and Medical Devices Agency, dated January 31, 2020), shall be entered with half-width alphanumeric characters/symbols (excluding “\$” if symbols are used) following “\$COMBI\$” and the half-width symbol “\$” shall be entered at the end (entry example; \$COMBI\$ABC123456\$).

(e) Narrative Case Summary and Further Information (H data elements)

For cases in Japan, enter “Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information (H.1),” “Reporter's Comments (H.2),” and “Sender's Comments (H.4)” in Japanese, and “Case Summary and Reporter’s Comments in Native Language (H.5.r)” does not need to be entered. For overseas cases, enter “Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information (H.1)” and “Reporter’s Comments (H.2)” in Japanese or English. Describe “Sender’s Comments (H.4)” in Japanese as the sender’s opinion.

○ Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information (H.1)

Describe in chronological order whenever possible. Enter information on health food, etc., if any.

○ Reporter’s Comments (H.2)

If there is no particular comment, state this.

○ Sender’s Comments (H.4)

- For overseas cases, enter the sender’s opinion, not the opinion of an overseas company. If the opinion of an overseas company has already been entered in “H.4,” describe the opinion of the overseas company and of the sender, separately.
- If some adverse reactions, etc. are no longer subject to reporting based on additional information, etc., briefly describe the contents.
- If it is unknown whether or not the report is on an in-house product and the report is made on the assumption that it is on an in-house product, state that.
- If an adverse reaction listed in “Other adverse reactions” is judged to be expected based on the description in the package insert, even though it is serious, describe the reason.
- If additional information cannot be obtained despite investigation, describe the reason and elements, etc. that were not available.

- If the sender's opinion is changed as a result of internal review by the marketing authorization holder or the foreign exceptional approval holder, describe the outline of the background.
  - If clinical laboratory values, etc. related to an adverse reaction, etc. could not be obtained, state this.
  - If the information on the assignment of the subject concerned cannot be revealed immediately for a compelling reason in a blinded post-marketing clinical study, etc., the first report on the occurrence of the adverse reaction, etc. concerned should be made even under blinded condition, with the reason why unblinding cannot be performed. In this case, enter the reason why unblinding cannot be performed in this element.
- (f) ICH ICSR Transmission Identification (BATCHWRAPPTER) (N.1 data elements)
- Date of Batch Transmission (N.1.5)  
When reporting by postal mail, etc., enter the date on which the report has been sent.

(2) Clinical trials

A. J data elements

(a) Identification Number (reporting category) (J2.1a)

When “Report Nullification / Amendment (C.1.11.1)” is reported as “2 = Amendment,” it will be regarded as an additional report. Therefore, as in the case with the usual additional report, the same reporting category as that of the previous report should be entered for reporting.

(b) Comment on Base Date for Reporting (J2.2.2)

Describe it in the following manner.

- When the “Date Report Was First Received from Source (C.1.4)” and the “Base Date for Reporting (J2.2.1)” are different for the first report.

Example)

- If a report is submitted again for the same case after the withdrawal report, summarize the background.
- If the case was originally not considered to be subject to an individual case safety report, but is found to be subject to the individual case safety report based on additional information, summarize the background.
- If the sender is aware of the fact that the reporting deadline specified in Article 273, Paragraph 1 or Paragraph 2 of the Regulation has passed, report that.

(c) Status Category of New Drugs, etc. (J2.4.k)

- For the approval status in Japan for the test drug or the ingredient identical to that of the test drug, select “3” (= unapproved) or “4” (= clinical trial for partial change ongoing) and enter it. “Clinical trial for partial change ongoing” means that a clinical trial for the change of administration route, addition of indication, addition of dosage form, etc. for the same ingredient as that of an approved drug is being conducted or all clinical trials related to the test drug concerned have been completed and the application for the partial change, etc. of approved product information is being prepared or has been filed.
- For study drugs other than the test drug, select “8” (= approved in Japan [excluding the test drug]) or “9” (= not approved in Japan [excluding the test

drug]) and enter it.

- When withdrawing the report based on additional information, the applicable category should also be entered.

(d) Future Actions (J2.10)

For overseas cases, enter the sender's actions, not the actions of an overseas company. This element should be entered from the first report.

State that measures such as reporting to medical institutions, revision of the informed consent form, revision of the protocol, revision of PRECAUTIONS, revision of the summary of approval application data (draft PRECAUTIONS, etc.), etc. have been taken or are scheduled to be taken in the future. For reporting to medical institutions, state the means (sending of communication documents, provision of revised Investigator's Brochure, etc., telephone communication, etc.) as well.

(e) Other Reference Matters, etc. (J2.11)

Describe other reference matters in the following order.

- If multiple suspected drugs subject to reporting are to be written in one report, status of expected/unknown shall be entered for each adverse reaction, etc. for each suspected drug subject to reporting.
- When reporting the same adverse reactions, etc. as those reported previously, enter the cumulative number of reports for each suspected drug subject to reporting.
- Regarding the free text elements, if another completion report is made after the completion report and there are additions/changes from the previous report in the free text elements, briefly describe the additions/changes in the free text elements.
- Descriptions in PRECAUTIONS, summary of approval application data, or Investigator's Brochure related to the report
- If a clinical trial for application for partial change in approved product information is conducted and overseas cases reported as post-marketing reports of adverse reactions, etc. are also reported as reports of adverse reactions, etc. in clinical trials, report the fact that they have already been submitted or will be submitted in "overseas adverse reaction reports (post-marketing)" or "overseas infection reports (post-marketing)."
- Other necessary items (e.g., if the report is an immediate report, state this; if an immediate report [report of adverse reactions, etc. in clinical trials] was made by e-mail, etc., state the fact that an immediate report [report of adverse reactions, etc. in clinical trials] was made and the date of report; state the fact that the adverse reaction was collected while reporting of adverse reactions, etc. was withheld, etc.)

(f) Test Substance Identification Code (J2.12)

Enter the test substance identification code of the main test drug described in the clinical trial notification. If no clinical trial notification has been submitted, enter the development code included in the protocol. Even if only the study drugs other than the main test drug correspond to suspected drugs, enter the test substance identification code of the main test drug stated in the notification of the clinical trial concerned, in "Test Substance Identification Code (J2.12)."

(g) Outline of Clinical Trial in Japan (J2.13)

Enter "Number of Notifications (J2.13.r.1)" and "Presence or Absence of Cases Being Treated (J2.13.r.4)" for each clinical trial of the main test drug. Enter "Presence

or Absence of Cases Being Treated (J2.13.r.4)” based on the information on the study drugs. However, if a report on adverse reactions, etc. is made on the day of submission of the clinical trial notification, enter “Target Disease (J2.13.r.2)” and “Development Phase (J2.13.r.3)” as well. The outline of the most recent clinical trial should be described even if clinical trials have been completed and the application is being prepared or has been filed, or even if the clinical trial period is over. If submission of a clinical trial notification is not required, leave “Number of Notifications (J2.13.r.1)” blank, and enter the contents described in the protocol in “Target disease (J2.13.r.2)” and “Development Phase (J2.13.r.3).” The information on the study in which the subject concerned is participating, enter “\$TT\$” in half-width alphanumeric characters in “Target Disease (J2.13.r.2).” If the target disease needs to be entered in “Target Disease (J2.13.r.2)” when, for example, no clinical trial notification is required, enter the target disease after “\$TT\$.”

B. E2B data elements

(a) Identification information (C data elements)

○ Worldwide Unique Case Identification Number (C.1.8.1)

If a clinical trial for application for partial change in approved product information is conducted and overseas cases reported as post-marketing reports of adverse reactions, etc. are also reported as reports of adverse reactions, etc. in clinical trials, enter “Worldwide Unique Case Identification Number (C.1.8.1)” stated in the post-marketing report of adverse reactions, etc.

○ Report Nullification / Amendment (C.1.11.1)

When this element is reported as “2 = Amendment,” the report will be regarded as an additional report, and therefore, it shall be handled as is the case with a usual additional report.

○ Study Type Where Reaction(s) / Event(s) Were Observed (C.5.4)

“Study Type Where Reaction(s) / Event(s) Were Observed (C.5.4)” needs to be provided if “Type of report (C.1.3)” is “2 = Report from study.”

(b) Patient characteristics (D data elements)

○ Patient (D.1)

Enter subject number or initials in Roman characters (half-width). In principle, a period (half-width, “.”) shall be placed after each Roman character. For overseas cases, it is basically acceptable to use the sent initials as they are.

○ Reported Cause(s) of Death (free text) (D.9.2.r.2)

Describe in Japanese for cases in Japan and in Japanese or English for overseas cases.

(c) Reaction(s) / Event(s) (E data elements)

○ Reaction / Event as Reported by the Primary Source in Native Language (E.i.1.1a)

When the name of the adverse reaction reported by the primary information source is different from the MedDRA term entered in “Reaction / Event (MedDRA code) (E.i.2.1b),” this element needs to be entered.

(d) Drug(s) Information (G data elements)

If information on health food, etc. is available, it should not be described in Drug(s) Information (G data elements), but described in Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant

Information (H.1).

- Characterisation of Drug Role (suspected drug/concomitant drug/interaction) (G.k.1)

This element should be entered for all study drugs and other drugs. If suspected drugs are different for respective multiple adverse reactions, etc., select “1” or “3” for each suspected drug for each adverse reaction, etc.

- Medicinal Product Name as Reported by the Primary Source (G.k.2.2)

[1] Study drugs

- In the case of a test drug with an active ingredient not approved in Japan, enter the test substance identification code.
- For study drugs with the same ingredients as drugs approved in Japan, enter the applicable re-examination code (9 digits) for prescription drugs and the applicable drug brand code (12 digits) for drugs requiring guidance or over-the-counter drugs, paying attention to differences in dosage forms, etc. For drugs such as generic drugs, for which no 9-digit re-examination code has been given, but a 7-digit re-examination code is known, be sure to enter the 7-digit re-examination code in this element in addition to “Substance / Specified Substance Name (G.k.2.3.r.1).”
- For study drugs corresponding to foreign pharmaceuticals other than test drugs as well, enter a 9-digit or 7-digit (for prescription drugs) or 12-digit (for drugs requiring guidance or over-the-counter drugs) code whenever possible. If there is no 9-digit re-examination code or 9-digit re-examination code is unknown, but a 7-digit re-examination code is known, be sure to enter the 7-digit re-examination code in this element in addition to entering it in “Substance / Specified Substance Name (G.k.2.3.r.1).” Enter the brand name if the code is unknown. If neither is known, available information such as generic name shall be provided in Japanese or English.
- In the case of study drugs not approved in Japan excluding test drugs, enter the overseas brand name in half-width alphanumeric characters.
- When reporting a case for which it cannot be determined whether the suspected drug is a test drug or comparator because the study has not been unblinded, enter “true” in “Investigational Product Blinded (G.k.2.5),” and information on the test drug in the elements included in “Drug Identification (G.k.2),” and the name of the comparator in “Other Reference Matters, etc. (J2.11).”

[2] Other drugs

- If the brand name cannot be identified, either the therapeutic category number or Japanese name may be entered.
  - For overseas cases, it is acceptable to enter an English name.
- Substance / Specified Substance Name (G.k.2.3.r.1)

[1] Study drugs

- If a generic name has been determined for a test drug that has not been approved in Japan, the generic name shall be provided. Enter the JAN (Japanese Accepted Names for Pharmaceuticals) preferentially. If the JAN has not been determined, it is acceptable to enter the names such as the INN (International Nonproprietary Names for Pharmaceutical Substances) in half-width alphanumeric characters.

- If no generic name has been specified for a test drug that has not been approved in Japan, the test substance identification code shall be provided. In this case, describe the mechanism of action, etc. of the test drug in “H.4 Sender’s comments.”
- For study drugs with the same ingredients as drugs approved in Japan, enter the re-examination code (7 digits) if they are prescription drugs. For over-the-counter drugs and drugs requiring guidance, the drug brand code table (12 digits) can be used.
- For combination drugs, enter the generic name of the active ingredient, in principle. It is also acceptable to enter the applicable code using re-examination code (7 digits), drug brand code table (12 digits), or therapeutic category code (3 digits).

[2] Other drugs

- If the generic name is unknown, either Japanese name or therapeutic category number may be entered. For overseas cases, it is acceptable to enter an English name.

○ Dose (G.k.4.r.1)

Enter the dose per administration. If the dose per administration is unknown but the daily dose is known, enter the daily dose in this element and 1 day in Definition of the Time Interval Unit (G.k.4.r.3).

○ Duration of Drug Administration (number) (G.k.4.r.6a)

When entering the number of days, the start date of administration should be considered as “1” to count the days.

○ Pharmaceutical Dose Form (free text) (G.k.4.r.9.1)

This element should be entered in half-width alphabet characters according to Appendix 7, “List of Dosage Forms,” of 2020 E2B (R3) Two Director Notification.

○ Route of administration TermID (G.k.4.r.10.2b)/Parent Route of Administration TermID (G.k.4.r.11.2b)

These elements shall be described in half-width numeric characters according to the ICH E2B code list in Appendix I (F) of Attachment 1 of E2B (R3) Implementation Guide Notification. If there is no appropriate route of administration in the code list, select “050 = Other.” “Route of Administration (free text) (G.k.4.r.10.1)” or “Parent Route of Administration (free text) (G.k.4.r.11.1)” should be described in Japanese for the cases in Japan, and in Japanese or English for the overseas cases.

○ Drug-Reaction(s) / Event(s) Matrix (G.k.9.i)

Describe at least study drugs among suspected drugs.

(e) Narrative Case Summary and Further Information (H data elements)

For cases in Japan, enter “Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information (H.1),” “Reporter’s Comments (H.2),” and “Sender’s comments (H.4)” in Japanese, and “Case Summary and Reporter’s Comments in Native Language (H.5.r)” does not need to be entered. For overseas cases, enter “Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information (H.1)” and “Reporter’s Comments (H.2)” in Japanese or English. Describe “Sender’s comments (H.4)” in Japanese as the opinion of the reporting company.

○ Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and

#### Additional Relevant Information (H.1)

Describe in chronological order whenever possible. Enter information on health food, etc., if any.

#### ○ Reporter's Comments (H.2)

If there is no particular comment, state this.

#### ○ Sender's Comments (H.4)

- This element should be entered from the first report. For overseas cases, enter the sender's opinion, not the opinion of an overseas company. If the opinion of an overseas company has already been entered in "H.4," describe the opinion of the overseas company and of the sender, separately.
- If no generic name has been determined for the test drug, describe the mechanism of action, etc. of the test drug.
- If some adverse reactions, etc. are no longer subject to reporting based on additional information, etc., briefly describe the contents.
- If additional information cannot be obtained despite investigation, describe the reason and elements, etc. that were not available.
- If clinical laboratory values, etc. related to an adverse reaction, etc. could not be obtained, state this.

### (3) Reports of adverse reactions to quasi-drugs, etc.

- [1] The guidelines for description of each element are shown below. Refer to E2B (R3) Implementation Guide Notification and 2020 E2B (R3) Two Director Notification as well. For the elements to be described by selecting a code among J data elements or E2B data elements, refer to the latest version of the code list that will be posted on the SKW site.

The elements are shown in the order of element numbers stated in Appendix 4 of the 2020 E2B (R3) Two Director Notification and E2B (R3) Implementation Guide Notification. For reference, the element names in the attached forms for quasi-drugs, etc. are also shown.

#### A. J data elements

##### (a) Identification Number (reporting category) (J2.1a)/identification number

If the in-house product is considered to be most closely causally related to the reported adverse reaction in light of medical/pharmaceutical knowledge, etc. (hereinafter referred to as the "primary suspected product") among the products for which causal relationship with the reported adverse reaction cannot be ruled out (hereinafter referred to as the "suspected products") is a quasi-drug, select "BA," and if the primary suspected drug is a cosmetic, select "BB" from the code list, "J2.1a Identification Number (reporting category)" in Appendix 5 of the 2020 E2B (R3) Two Director Notification, "Code Values of Data Elements for Management of Systems of the Ministry of Health, Labour and Welfare (J data elements)."

- The brand name of the primary suspected product cannot be identified, and the series name (a specific name that refers to a group of approved or notified products; the same applies hereinafter; note that it is different from the brand name of a "series product" shown in PAB/ELD Notification No. 231 dated March 29, 1994) is used for reporting, select "BA" for this element if both quasi-drugs and cosmetics are included in the series concerned.

##### (b) Identification Number (number) (J2.1b)/identification number

The identification number will be given after PMDA receives the first report of the case concerned. Therefore, only the reporting category shall be entered in the first report, and the number part will be left blank. The second and subsequent reports shall be made by entering the identification number shown in “Local Report Number (ACK.B.r.2)” in the acknowledgement message (hereinafter referred to as the “ACK message”) sent from PMDA.

(c) Base Date for Reporting (J2.2.1)/base date for reporting

Enter the base date for reporting for the report concerned. Usually, it is the date when the matters specified in Article 228-20, Paragraph 5 of Regulation are learned.

(d) Comment on Base Date for Reporting (J2.2.2)/comment on base date for reporting

If explanation of the information on the Base Date for Reporting (J2.2.1) is necessary, such as the following cases, enter it:

- When the Date Report Was First Received from Source (C.1.4) and the Base Date for Reporting (J2.2.1) are different in the first report;
- When the marketing authorization holder or foreign exceptional approval holder is aware of the fact that the reporting deadline specified in Article 228-20, Paragraph 5 of Regulation has passed; and
- When the case was originally considered to be subject to reporting within 30 days, but is found before the initial report to be subject to reporting within 15 days based on additional information.

(e) Status Category of New Drugs, etc. (J2.4.k)/in-house products

For in-house products among suspected products, select “5 = Not applicable” from the code list of “J2.4.k Status Category of New Drugs, etc.” in Appendix 5 of 2020 E2B (R3) Two Director Notification. Leave this element blank for other companies' products and concomitant products.

(f) Complete / Incomplete Category (J2.7.1)/completion report and incompleteness report

If the investigation for the reported case has been completed, select “completed = completed.” If the investigation has not been completed, select “active = not completed.” If any new information is obtained after the completion report, a new completion report should be made.

(g) Comments on Incompletion (J2.7.2)/completion report and incompleteness report

If the report is incomplete, provide the reason why the investigation has not been completed.

(h) Flag for Not Subject to Reporting (J2.8.1)/not subject to reporting

When making an additional report on cases not subject to reporting, select “1 = Not subject to reporting.” See Attachment 4 for details of additional reports on cases not subject to reporting.

(i) Reason for Not Subject to Reporting (J2.8.2)/not subject to reporting

Provide the reason for making an additional report on cases not subject to reporting.

(j) Future Actions (J2.10)/future actions

In this element, actions based on the evaluation of the reported adverse reaction and actions in future post-marketing safety management shall be described. If the sender considers it necessary to revise PRECAUTIONS, etc., the sender should consult the Office of Pharmacovigilance I, PMDA, separately.

(k) Other Reference Matters, etc. (J2.11)/other reference matters, etc.

Describe other reference matters shown below.

- Status of description, etc. of PRECAUTIONS  
If the reporting deadline is in 15 days or 30 days and the event is determined as known based on the description in “PRECAUTIONS,” the description status shall be stated.
- If the reported case is a case of an adverse reaction, etc. reported by a medical institution which has been notified by PMDA to a marketing authorization holder, etc., enter the “receipt number” under this system along with the fact that it is a “case reported by a medical institution.”
- If there is a suspected product to be reported by the name of the series, state that the brand name has not been identified along with the name of the series. If a suspected product of another company is reported with a series name and it is difficult to select a representative product from the series, report that.
- If there are any other reference matters related to the reported case, describe them in this element.
- (l) Receiver’s Organization Name (J2.18.1)  
Enter “Pharmaceuticals and Medical Devices Agency.”
- (m) Receiver’s title (J2.18.2)  
Enter “Chief Executive.”
- (n) Receiver’s Last Name (J2.18.3)  
Enter the last name of the Chief Executive of PMDA.
- (o) Receiver’ First Name (J2.18.4)  
Enter the first name of the Chief Executive of PMDA.
- (p) Remarks (J2.19)  
Enter the version of the code list package for J data elements and E2B data elements in the e-mail or paper-based reports. See 5 for details of versions.
- (q) Nickname (J2.23.k)/nickname  
If there is a nickname printed on the immediate container, etc. of the suspected product and the nickname is widely recognized by consumers, enter it. Leave this element blank if not applicable.
- (r) Product Type (J2.24.k)/product type
  - Select the applicable product type for each suspected product from the code list for “J2.24.k Product Type” in Appendix 5 of 2020 E2B (R3) Two Director Notification. If the product type of a suspected product of another company is unknown, enter “c01” when the product concerned is a quasi-drug and “c02” when the product concerned is a cosmetic.
  - When a suspected product is reported with a series name, the description shall be handled as shown in [1] to [3] below.
    - [1] If the series concerned consists of products of a single product type, enter the applicable product type.
    - [2] If the series concerned consists of products of multiple product types, handle this element as shown in the table below.

Series composition	Description of “Product Type”
When the series consists only of quasi-drugs	Enter “c01”
When the series consists only of cosmetics	Enter “c02”
When the series consists of quasi-drugs and cosmetics	Enter “c01”

[3] If a suspected product of another company is reported with a series name, the element shall be handled in the same way as shown in [1] and [2] above. However, if detailed information on products constituting the series concerned has not been obtained and it is difficult to select one from the code list, enter “c03.”

(s) Ingredient Category (J2.25.k.r)/product ingredient

For all the ingredients listed in “Substance / Specified Substance Name (G.k.2.3.r.1),” select “1 = Active ingredient” if it corresponds to an active ingredient and “2 = Other ingredient” if it corresponds to ingredients other than the active ingredient.

(t) Seriousness, etc. (J2.26.i)/category of seriousness

Select the applicable seriousness, etc. for each adverse reaction from the code list for “J2.26.i Seriousness, etc.” in Appendix 5 of 2020 E2B (R3) Two Director Notification.

(u) Date Flag (J2.27.r), Information Source (J2.29.r)/information source

Regarding the information on the Date Report Was First Received from Source (C.1.4) and the Date of Most Recent Information for This Report (C.1.5), select the corresponding date flag from “J2.27.r Date Flag” in Appendix 5 of 2020 E2B (R3) Two Director Notification (“1 = Date on which first report was received” or “2 = Date of most recent information for this report”). In addition, select the source of information on each date of obtaining information from “J2.29.r Information source” in Appendix 5 of 2020 E2B (R3) Two Director Notification. If information is received from multiple sources on the same day, all sources of information should be listed along with date flags.

Example)

r*	Date Report Was First Received from Source (C.1.4)	Information Source (J2.29.r)	Date Flag (J2.27.r)
r = 1	20170401	Patient	1 = Date on which first report was received
r = 2		Medical institution	1 = Date on which first report was received

r*	Date of Most Recent Information for This Report (C.1.5)	Information Source (J2.29.r)	Date Flag (J2.27.r)
r = 1	20170411	Medical institution	2 = Date of most recent information for this report
r = 2		Distributor	2 = Date of most recent information for this report

\*r indicates the repetition number of J2.29.r and J2.27.r.

r = 1 means the first repetition, r = 2 means the second repetition.

- (v) Presence or Absence of Pregnancy (J2.28)/presence or absence of pregnancy  
If the patient is female, select the presence or absence of pregnancy at the time of onset of the adverse reaction from “J2.28 Presence or Absence of Pregnancy” in Appendix 5 of 2020 E2B (R3) Two Director Notification. If it is unknown, select the applicable code from NullFlavor.

B. E2B data elements

Only the E2B data elements that should be noted in description are listed below. See Appendix 2 of 2020 E2B (R3) Two Director Notification for all the elements that need to be entered.

- (a) Date of Batch Transmission (N.1.5)/report date

Enter the date of this report. Enter the date of transmission in the case of electronic reporting, the date of shipment in the case of reporting by postal mail, etc., the date of submission at the reception in the case of reporting at the reception, and the date of e-mail transmission in the case of reporting by e-mail. Use the Western calendar for the year.

- (b) Message Sender Identifier (N.2.r.2)/sender identifier

Enter the sender identifier. If the sender identifier has not been registered with PMDA, make an application with reference to 9 of Attachment 9.

- (c) Sender’s (case) Safety Report Unique Identifier (C.1.1)/unique case number

The identifier shall be in the form of “Country code of the primary source-Sender identifier-Unique number,” and the unique number part shall be a unique number for each case such as an in-house control number. See the section for C.1.1 in Attachment 1 of the E2B (R3) Implementation Guide Notification for details of C.1.1.

- (d) Date Report Was First Received from Source (C.1.4)/date on which first report was received

Enter the date when the reporting company obtained the four minimum required pieces of information, etc. for the case concerned. See the Implementation Guide Notification for details on minimum required information. Use the Western calendar for the year.

- (e) Date of Most Recent Information for This Report (C.1.5)/date of most recent information for this report

Enter the latest date of obtaining information related to the reported case during the period up to submission of the report. Use the Western calendar for the year.

- (f) Are Additional Documents Available? (C.1.6.1)/attached documents

When submitting materials such as literature and various test results (X-ray, ECG, etc.) related to the report concerned (hereinafter referred to as the “submission data”) with the report, select “true = present.” When there are no submission data, select “false = absent.” Do not include the status of attachment of the description on immediate containers, etc. and a copy of description in package insert, etc. in this element.

- (g) Documents Held by Sender (C.1.6.1.r.1)/attached documents

Enter names of materials other than literature, such as various test results related to the report concerned. The titles of literature shall be entered in “Literature Reference(s) (C.4.r.1).”

- (h) Included Documents (C.1.6.1.r.2)/ attached documents

The materials corresponding to the material names listed in C.1.6.1.r.1 may be

attached to this element. See Attachment 7 for details.

- (i) Does This Case Fulfil the Local Criteria for an Expedited Report? (C.1.7)/reporting deadline of 15 or 30 days

When the report concerned is based on Article 228-20, Paragraph 5, Item 1 of the Regulation, select “true = 15 days.” When the report concerned is based on Item 2 (a) of the same paragraph, select “false = 30 days.”

- (j) Report Nullification / Amendment (C.1.11.1)/report withdrawal

When withdrawing the report, select “1 = Nullification” for this element. See Attachment 4 for details of withdrawal reports and additional reports on cases not subject to reporting. If “2 = Amendment” is selected and reported, the report will be handled as a usual additional report.

- (k) Reason for Nullification / Amendment (C.1.11.2)/report withdrawal

Provide the reason for withdrawing the report

- (l) Sender Type (C.3.1)

Marketing authorization holders of quasi-drugs or cosmetics shall select “1 = Pharmaceutical Company.”

- (m) Sender’s Organisation (C.3.2)

Enter the sender identifier.

- (n) Sender’s Name (C.3.3.2 to C.3.3.5)/name

Enter the name of the corporation and the name and title of its representative.

- (o) Sender's Address (C.3.4.1 to C.3.4.3 and C.3.4.5)/address

Enter the location of the main office of the corporation.

- (p) Literature Reference(s) (C.4.r.1)/attached documents

Enter the titles of literature related to the report concerned.

- (q) Included (C.4.r.2)/attached documents

The literature corresponding to the literature titles entered in C.4.r.1 may be attached to this element. See Attachment 7 for details.

- (r) Patient (D.1)/patient initials

Enter the patient’s initials in half-width alphabet characters. In principle, put a period (half-width) “.” after an alphabet. If initials are unknown, select the applicable code from NullFlavor.

- (s) Age at Time of Onset of Reaction / Event (D.2.2a and D.2.2b), Patient Age Group (D.2.3)/age at time of onset of reaction

Enter the patient’s age at the time of onset of the adverse reaction. If detailed information cannot be obtained, it may be described which decade of age he/she is in. If the patient’s age and which decade of age he/she is in are unknown but the age group is known, select the applicable age group. If the element is blank, it is regarded as “unknown.”

- (t) Gestation Period When Reaction / Event Was Observed in the Foetus (D.2.2.1a, D.2.2.1b)/gestational age

If a pregnant woman used the suspected product and an adverse reaction was observed in her or her fetus, enter the gestational age at the onset of the adverse reaction in this element. If the adverse reaction occurs in the mother, enter the age of the mother at the onset of the adverse reaction in patient’s age (D.2.2 or D.2.3), and enter the gestational age at the onset of the adverse reaction in this element. If the adverse reaction occurs in the fetus, enter the gestational age at the onset of the adverse reaction in this element. If gestational age is unknown, it can be left blank.

(u) Body Weight (D.3), Height (D.4)/body weight, height  
Enter the information on the patient's height and body weight at the time of onset of the adverse reaction. When entering numbers, round each number to the nearest whole number. If the element is blank, it is regarded as "unknown."

(v) Sex (D.5)/sex  
Select the patient's sex. If the element is blank, it is regarded as "unknown."

(w) Medical History and Concurrent Conditions (D.7.1.r.1b)/primary disease, complication, past history

Enter the primary disease, complications, or past history related to the reported adverse reaction using the LLT codes of the MedDRA terms. If the element is blank, it is regarded as "unknown."

(x) Continuing (D.7.1.r.3)/primary disease, complication, past history

Select "true" if the disease entered in D.7.1.r.1b was persisting at the onset of the adverse reaction; select "false" if the disease has resolved before then. If the element is blank, it is regarded as "unknown."

(y) Text for Relevant Medical History and Concurrent Conditions (D.7.2)/primary disease/complication, past history, other notable matters

If other notable information such as information on the patient's allergy has been obtained, enter it in this element.

If there is no applicable MedDRA code for the primary disease, complication, or past history related to the reported adverse reaction, describe that in this element. Similarly, if there is no applicable MedDRA code for "Relevant past drug history, Reaction (D.8.r.7b)," describe that in this element.

Establish each item according to the following examples, and enter the content after the item name. As shown in the example, use the parentheses ([ ]) to enter the item, and use the same item names as those in the example. Even if there is no applicable information and the item is left blank, the item must be entered.

Example)

[Primary disease/complication] Allergic rhinitis, conjunctivitis

[Past history] Atopic dermatitis

[History of adverse reactions] ○○ ointment/rash, □□ soap/itching

[Allergy] Cedar pollen, mites, dust

[Other] △△△•••

(z) Relevant past drug history, Name of Drug as Reported (D.8.r.1), Reaction (D.8.r.7b)/history of adverse reactions

If the patient has experienced any adverse reaction to a drug, quasi-drug, or cosmetic before the onset of the reported adverse reaction, enter the brand name, etc. of the product considered to be the cause of the adverse reaction, and the adverse reaction that occurred using the LLT code of MedDRA terms. If the history is unknown, leave D.8.r.1 and D.8.r.7b blank. If the patient has a history of an adverse reaction but there is no corresponding MedDRA code, leave D.8.r.1 and D.8.r.7b blank, and enter the name of the adverse reaction along with the applicable brand name, etc. in the "Text for Relevant Medical History and Concurrent Conditions (D.7.2)." If there is a history of an adverse reaction that can be expressed by a MedDRA code, but the name of the drug or product used is unknown, select NullFlavor = UNK for D.8.r.1.

(aa) Reaction / Event as Reported by the Primary Source in Native Language (E.i.1.1a)/name of adverse reaction or symptom, abnormal finding

Regarding an adverse reaction considered to have been caused by the primary suspected product in the report concerned entered in “Reaction / Event (E.i.2.1b),” if there is neither a MedDRA code corresponding to the name of the adverse reaction nor corresponding code in “Codes of adverse reactions to quasi-drugs, etc.” shown in Appendix 8 of 2020 E2B (R3) Two Director Notification, enter an appropriate name of adverse reaction from a medical point of view in this element.

(bb) MedDRA version for Reaction / Event (E.i.2.1a)/MedDRA version

When entering the adverse reaction name in the MedDRA code, enter the version of the code used.

(cc) Reaction / event (E.i.2.1b)/MedDRA code/quasi-drug, etc., codes of adverse reactions to quasi-drugs, etc.

- Enter the MedDRA LLT code corresponding to the name of the adverse reaction or a code in the Code of adverse reaction to quasi-drug, etc. from Appendix 8 of 2020 E2B (R3) Two Director Notification in E.i.2.1b. If there are multiple adverse reactions in a report, use either MedDRA terms or terms shown in the table of the Codes of adverse reactions to quasi-drug, etc. consistently throughout the report. If there is no appropriate MedDRA term or code in the Codes of adverse reactions to quasi-drug, etc., leave this element blank, and enter the adverse reaction name in “Reaction / Event as Reported by the Primary Source in Native Language (E.i.1.1a)” after determining the appropriate adverse reaction name from a medical point of view.
- The Codes of adverse reactions to quasi-drug, etc. are updated appropriately on the SKW site. For reporting, refer to the latest version.

(dd) Date of Start of Reaction / Event (E.i.4)/onset date

Enter the date of onset of the adverse reaction. Use the Western calendar for the year. If the exact date cannot be obtained, it is acceptable to enter the year of onset or the year and month of onset of the adverse reaction. If the date is unknown, select the applicable code from NullFlavor.

(ee) Date of End of Reaction / Event (E.i.5)/date of outcome

If the outcome of an adverse reaction is “recovered/resolved” or “recovering/resolving,” enter the date on which the adverse reaction is assessed as “recovered/resolved” or “recovering/resolving.” If the outcome is “death,” enter the date of death. Use the Western calendar for the year. If the exact date cannot be obtained, it is acceptable to enter the year of outcome or the year and month of outcome of the adverse reaction. If the date is unknown, select the applicable code from NullFlavor.

(ff) Outcome of Reaction / Event at the Time of Last Observation (E.i.7)/outcome

Select and enter the outcome of the adverse reaction. If the outcome corresponds to “4 = recovered/resolved with sequelae,” enter detailed information on sequelae in “Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information (H.1).”

(gg) Characterisation of Drug Role (G.k.1)/brand name and nickname of the product, other drugs, quasi-drugs, cosmetics, etc. used concomitantly

Select “1 = Suspect” for the suspected product and “2 = Concomitant” for concomitant products. Select “3 = Interacting” for products whose interaction with

other products is suspected to have caused the adverse reaction.

(hh) Medicinal Product Name as Reported by the Primary Source (G.k.2.2)/brand name and nickname of the product, other drugs, quasi-drugs, cosmetics, etc. used concomitantly

- Provide the product code of the primary suspected product first. Then, regardless of whether the products are in-house products or products of other companies, enter the suspected products in the descending order of the level of suspicion concerning the relationship with the onset of the adverse reaction.
  - If there are quasi-drugs, cosmetics, etc. used at the onset of the adverse reaction that are not considered related to the adverse reaction, enter them as concomitant products after suspected products.
  - Provide the product codes for suspected in-house products. If the product cannot be identified despite the efforts to do so, it is acceptable to enter the code of the series. Provide the code of the smallest unit of the series identified.
  - See 8 of Attachment 9 for how to apply for product codes.
  - For other companies' products and concomitant products, it is acceptable to enter the brand name or series name, instead of the code.
  - When entering information in the attached forms for quasi-drugs, etc. in paper-based reporting and reporting by e-mail, enter the brand name or series name along with a code for in-house suspected products.
  - When a suspected product is reported with a series name, it shall be stated in "Other Reference Matters, etc. (J2.11)" that the brand name has not been identified, along with the series name.
- (ii) Substance / Specified Substance Name (G.k.2.3.r.1)/ingredients of product
- For each suspected product entered in "Medicinal Product Name as Reported by the Primary Source (G.k.2.2)," repeat this element and enter all ingredients including the active ingredient and additives.
  - If it is difficult to know all ingredients in the suspected products of other companies, entry of the ingredients to the extent they are known is acceptable. The element can be left blank if no information is obtained, but efforts shall be made to obtain information.
  - When reporting a suspected product with a series name, enter all the ingredients of the representative product in the series concerned. If there are any quasi-drugs in the series concerned, select a representative product among the quasi-drugs.
  - If a suspected product of another company is reported with a series name and it is difficult to select a representative product from the series, the element can be left blank. This shall be stated in "Other Reference Matters, etc. (J2.11)" that it was difficult to select a representative product.

(jj) Authorisation / Application Number (G.k.3.1)/approval number

Enter the approval number of the primary suspected product. If the primary suspected product is a cosmetic subject to marketing notification or a quasi-drug requiring no approval, or if the primary suspected product is reported with a series name, this element can be left blank.

(kk) Dose (G.k.4.r.1)/amount used per day

In principle, enter the amount used per day. If the amount used per day cannot be expressed using units (mL, number of bottles, number of items, number of sheets, etc.), leave this element blank and describe it in "Dosage Text (G.k.4.r.8)" indicating

specific amount of use. If G.k.4.r.1 and G.k.4.r.8 are blank, these elements are regarded as “unknown.”

(ll) Number of Units in the Interval (G.k.4.r.2), Definition of the Time Interval Unit (G.k.4.r.3)/amount used per day

If the product was used every day, enter “1” in G.k.4.r.2 and “Day” in G.k.4.r.3. If the product was not used every day, leave these elements blank and enter the dosing interval in G.k.4.r.8. If G.k.4.r.2, G.k.4.r.3, and G.k.4.r.8 are blank, these elements are regarded as “unknown.”

(mm) Date and Time of Start of Drug (G.k.4.r.4), Date and Time of Last Administration (G.k.4.r.5)/duration of use (start date to end date)

Provide the start and end dates of the use of the suspected product. Use the Western calendar for the year. If the exact date cannot be obtained, it is acceptable to enter the year or the year and month of the start and end of the use. If the date is unknown, select the applicable code from NullFlavor. If the suspected product is still being used, enter the name of the suspected product concerned and state that the product is still being used in “Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information (H.1).”

(nn) Dosage Text (G.k.4.r.8)/amount used per day

If the amount used per day cannot be expressed using units (mL, number of bottles, number of items, number of sheets, etc.), describe the amount in this element indicating specific amount of use (e.g., size of a 500 yen coin, pearl-sized amount). If G.k.4.r.1 to G.k.4.r.3 and G.k.4.r.8 are blank, these elements are regarded as “unknown.”

If the amount used may have affected the onset or seriousness of the adverse reaction, such as excessive use, this should be described in “Sender’s comments (H.4)” and the details of the use status should be described in “Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information (H.1).”

(oo) Route of Administration (G.k.4.r.10.1)/route and site of use

For products to be orally administered such as health drinks, enter “Oral.” For topical cosmetics, etc., enter the site of use by the patient (e.g., face, arms, whole body, etc.). If it is unknown, select the applicable code from NullFlavor.

(pp) Did Reaction Recur on Re-administration? (G.k.9.i.4)/re-use, recurrence

Select the appropriate status of re-use of the primary suspected product after the onset of the reported adverse reaction. Leave it blank if it is unknown whether the product was used again. If the element is blank, it is regarded as “unknown.”

If recurrence is “present,” information on the adverse reaction at the time of recurrence and its course, etc. should be described in “Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information (H.1).”

(qq) Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information (H.1)/onset of adverse reaction and course of treatment, etc.

- Describe briefly the use status of the suspected product (start date of use, end date of use, etc.), occurrence status of the adverse reaction (onset date, site of onset, etc.), information on the procedure, etc. at medical institutions (various test results, date of hospitalization, etc.), etc. in chronological order.

- Regarding the use of the suspected product, if the amount used possibly affected the onset or seriousness of the adverse reaction, such as excessive use, describe the details of the status of use.
- (rr) Reporter's Comments (H.2)/reporter's comments, etc.
  - Describe the view of the physician involved in the reported adverse reaction (the physician involved in diagnosis, treatment, etc. of the adverse reaction; the same applies hereinafter) and diagnostic information. If the physician's view cannot be obtained because the patient has not visited a medical institution for other reasons, report this.
  - Describe the physician's evaluation of the causal relationship between the use of the suspected in-house product and the adverse reaction.
- (ss) Sender's Comments (H.4)/sender's comments, etc.
  - Describe the company's evaluation of the causal relationship between the use of the suspected in-house product and the adverse reaction.

### 3. Description in research reports and foreign corrective action reports

#### (1) Post-marketing (excluding quasi-drugs, etc.)

##### A. J data elements

For the following (a) to (c), see 2 (1) A. (a) to (c) above.

- (a) Identification Number (reporting category) (J2.1a)
- (b) Comment on Base Date for Reporting (J2.2.2)
- (c) Status Category of New Drugs, etc. (J2.4.k)
- (d) Future Actions (J2.10)

In this section, actions based on the sender's evaluation of the research report or foreign corrective action report concerned, necessity of information provision such as revision of the package insert, etc. shall be described. For overseas cases, enter the sender's actions, not the actions of an overseas company. If the sender considers it necessary to revise PRECAUTIONS, etc., the sender should consult the Office of Pharmacovigilance I or the Office of Pharmacovigilance II, PMDA (the Office of Manufacturing Quality and Vigilance for Medical Devices in the case of in vitro diagnostics), separately.

#### (e) Other Reference Matters, etc. (J2.11)

Describe other reference matters.

- Research reports

As for the description of "Status of description of PRECAUTIONS," describe the PRECAUTIONS at the time of reporting for the drug subject to reporting.

When a research report related to the previously distributed Dear Healthcare Professional Letters of Emergent Safety Communications or Dear Healthcare Professional Letters of Rapid Safety Communications is to be made, enter the date and number of the PSEHB/SD Order for the Dear Healthcare Professional Letters of Emergent Safety Communications or Dear Healthcare Professional Letters of Rapid Safety Communications.

- Foreign corrective action reports

As for the description of "Status of description of PRECAUTIONS," describe the PRECAUTIONS at the time of reporting for the drug subject to reporting.

When a foreign corrective action report related to the previously distributed Dear

Healthcare Professional Letters of Emergent Safety Communications or Dear Healthcare Professional Letters of Rapid Safety Communications is to be made, enter the date and number of the PSEHB/SD Order for the Dear Healthcare Professional Letters of Emergent Safety Communications or Dear Healthcare Professional Letters of Rapid Safety Communications. If sufficient information was not obtained, report this.

B. E2B data elements

See 2. (1) B above for details. Pay attention to the following points.

○ Additional Information on Drug (G.k.11)

In a report of malfunction of the machine/equipment part of a combination product, enter “\$COMBI\$” using half-width symbols and half-width alphabet capital letters.

(2) Clinical trials

A. J data elements

For the following (a) to (c), see 2 (2) A. (a) to (c) above.

(a) Identification Number (reporting category) (J2.1a)

(b) Comment on Base Date for Reporting (J2.2.2)

(c) Status Category of New Drugs, etc. (J2.4.k)

(d) Future Actions (J2.10)

Describe the actions based on the sender's evaluation of the research report or foreign corrective action report concerned, necessity of changes in the clinical trial plan or information provision to the medical institution participating in the clinical trial, etc. For overseas cases, enter the sender's actions, not the actions of an overseas company.

(e) Other Reference Matters, etc. (J2.11)

Describe other reference matters.

○ Research reports

The status of description of informed consent form, protocol, PRECAUTIONS, summary of data for approval application (draft PRECAUTIONS, etc.), etc. and other necessary matters (e.g., the fact that the research report is based on the data collected while reporting of adverse reactions, etc. was withheld, etc.) shall be described. If sufficient information was not obtained, report this. When an additional report is made for reasons including new information, the changes from the previous report should be shown with the reasons for the changes.

○ Foreign corrective action reports

Describe the status of description of informed consent form, protocol, PRECAUTIONS, summary of data for approval application (draft PRECAUTIONS, etc.), etc. and other necessary matters (e.g., if the report is an immediate report, that effect; if an immediate report [report of adverse reactions, etc. in clinical trials] was made by e-mail, etc., the fact that an immediate report [report of adverse reactions, etc. in clinical trials] was made and the date of the report; the fact that the corrective action report was collected while reporting of adverse reactions, etc. was withheld, etc.). If sufficient information was not obtained, report this. When an additional report is made for reasons including new information, the changes from the previous report should be shown with the reasons for the changes.

(f) Outline of Clinical Trial in Japan (J2.13)

Apply 2. (2) A. (g) above with modifications.

- B. E2B data elements  
See 2. (2) B. above.

(3) Research reports of quasi-drugs, etc.

- A. J data elements

For the following (a) to (k), see each applicable element in 2. (3) A. above.

- (a) Identification Number (reporting category/number) (J2.1a/J2.1b)
- (b) Base Date for Reporting (J2.2.1)
- (c) Comment on Base Date for Reporting (J2.2.2)
- (d) Status Category of New Drugs, etc. (J2.4.k)
- (e) Complete/Incomplete Category (J2.7.1)
- (f) Comments on Incompletion (J2.7.2)
- (g) Receiver's Organization Name (J2.18.1)
- (h) Receiver's title (J2.18.2)
- (i) Receiver's Last Name (J2.18.3)
- (j) Receiver's First Name (J2.18.4)
- (k) Ingredient Category (J2.25.k.r)
- (l) Future Actions (J2.10)

In this element, actions based on the sender's evaluation of the research report concerned, necessity of providing information such as revision of the package insert, etc. shall be described. If the sender considers it necessary to revise PRECAUTIONS, etc., the sender should consult the Office of Pharmacovigilance I, PMDA, separately.

- (m) Other Reference Matters, etc. (J2.11)

Describe other reference matters.

As for the description of "Status of description of PRECAUTIONS," describe the PRECAUTIONS at the time of reporting for the quasi-drug or cosmetic subject to reporting.

- (n) Country of Publication (J2.15.r)

Enter the country of the affiliation of the reporter/author, etc. of the literature or the study site by selecting an appropriate code from the country codes.

- (o) Key Points of Report (J2.16)

Key points of the contents described in "Summary of Research Reports or Actions Taken Overseas (H.1)" shall be shown in this element. For clinical studies/research, include the study design (analytical method), subjects, comparator, name of ingredients, etc., and possible risks in the description. For nonclinical studies/research, include the animal species or the name of cells, and *in vivo/in vitro* in the description.

- (p) Study / Research Classification (J2.17.r)

Indicate whether the research report is on a clinical study/research or a nonclinical study/research by selecting either one of them.

- B. E2B data elements

Only the E2B data elements that should be noted in description are listed below. See Appendix 2 of 2020 E2B (R3) Two Director Notification for all the elements that need to be entered.

For the following (a) to (l), see each applicable element in 2. (3) B. above.

- (a) Message Sender Identifier (N.2.r.2)
- (b) Sender's (case) Safety Report Unique Identifier (C.1.1)
- (c) Date Report Was First Received from Source (C.1.4)
- (d) Date of Most Recent Information for This Report (C.1.5)
- (e) Report Nullification / Amendment (C.1.11.1)
- (f) Sender Type (C.3.1)
- (g) Sender's Organisation (C.3.2)
- (h) Sender's Name (C.3.3.2 to C.3.3.5)
- (i) Sender's Address (C.3.4.1 to C.3.4.3 and C.3.4.5)
- (j) Publication Status of Research Reports or Actions Taken Overseas (C.4.r.1)
- (k) Included (C.4.r.2)
- (l) Authorisation / Application Number (G.k.3.1)
- (m) Date of Batch Transmission (N.1.5)

Enter the date of this report. Enter the date of transmission in the case of electronic reporting, the date of shipment in the case of reporting by postal mail, etc., and the date of submission at the reception in the case of reporting at the reception. Use the Western calendar for the year.

- (n) Does This Case Fulfil the Local Criteria for an Expedited Report? (C.1.7)  
Select "false = 30 days."
- (o) Medicinal Product Name as Reported by the Primary Source (G.k.2.2)  
Provide the code of the product concerned issued by PMDA.  
See 8 of Attachment 9 for how to apply for product codes.
- (p) Substance / Specified Substance Name (G.k.2.3.r.1)  
For each suspected product subject to reporting, enter all ingredients including the active ingredient and additives.
- (q) Summary of Research Reports or Actions Taken Overseas (H.1)  
Describe briefly the contents of the research report concerned.
- (r) Sender's Comments (H.4)  
Describe the opinion that the research report concerned is subject to reporting. In addition, based on the contents of the research report, enter the evaluation by the sender regarding the product subject to reporting based on the presented results.

#### 4. Use of MedDRA

##### (1) Description of version

The ICSR file should contain the version used for reporting for each MedDRA version element. In addition, when the attached forms or the attached forms for quasi-drugs, etc. are submitted in paper-based reporting or reporting by e-mail, the version of MedDRA used for reporting shall be entered in the remarks column.

(2) Version update

Unless otherwise notified, PMDA accepts only the report using the latest version and the version immediately before that from the week after the version update. Therefore, promptly respond to the latest version.

5. Code system version

(1) Description of version

Each code list used for J data elements and E2B data elements (for J data elements, refer to Appendix 5 of the 2020 E2B (R3) Two Director Notification and SKW site; for E2B data elements, refer to Appendix I (F) of Attachment 1 of the E2B (R3) Implementation Guide Notification and SKW site) has an individually assigned code system version. The ICSR file should include the code system version used for reporting for each of J data elements or E2B data elements described with codes.

In addition, when preparing a report in a paper medium to be submitted in paper-based reporting or reporting by e-mail, etc., enter the version of each code list package used for reporting in the remarks column of the attached forms or the attached forms for quasi-drugs, etc. Code list package version refers to the version included in the zip file name of the code list posted on the SKW site. For example, if the file name of the code list used in for E2B data elements is “7\_E2B Bilingual Code Lists v2.9,” v2.9 is the version.

(2) Version update

The code system version of each code table is updated irregularly as needed. When switching the version of the code system, a transition period of about 2 months shall be set after publicizing it in advance, and both new and old versions can be accepted only during the transition period, and only the new version can be accepted after the end of the transition period. During the transition period, make sure to use the same version for each code table in one report. However, if multiple reports are submitted in a batch, individual reports within the batch may be in different versions.

**Handling of Withdrawal of Reports and Adverse Reactions, etc. No Longer Subject to Reporting (post-marketing) (excluding reports of adverse reactions to quasi-drugs, etc.)**

1. Handling of withdrawal of reports

(1) Reports subject to withdrawal

In principle, reports can be withdrawn only when any of the following [1] to [6] is met. However, if the withdrawal is judged to be inappropriate based on the inquiries, etc. about the contents of withdrawal from PMDA, actions such as re-reporting shall be taken.

When withdrawing a report, select “1 = Nullification” for “Report Nullification / Amendment (C.1.11.1),” enter the applicable reason among the following [1] to [6] in “Reason for Nullification / Amendment (C.1.11.2),” and select “Completed = completed” for “Complete / Incomplete Category (J2.7.1).” Do not enter anything in “Flag for Not Subject to Reporting (J2.8.1)” and “Reason for Not Subject to Reporting (J2.8.2).”

[1] When it is found that no in-house drug was administered in a case in Japan

[2] When it is found that neither in-house drug nor foreign pharmaceutical containing the same active ingredient as that in the in-house drug have been administered in an overseas case

[3] When the event is found to have occurred before administration of the drug (this does not apply for exacerbation)

[4] When the same information is found to have been reported in duplicate

[5] If the following elements are erroneously described:

“Identification Number (reporting category) (J2.1a)”

“Sender’s (case) Safety Report Unique Identifier (C.1.1)”

“Worldwide Unique Case Identification Number (C.1.8.1)”

“First Sender of This Case (C.1.8.2)”

[6] When there is no case

(2) Re-reporting after withdrawal of the report

If any additional information on the case concerned is obtained after withdrawing the report and re-reporting is required, the initial report (first report) shall be prepared with attention paid to the following points.

[1] Identification Number (reporting category) (J2.1a)

Enter the applicable reporting category.

[2] Identification number (number) (J2.1)

Leave it blank.

[3] Date Report Was First Received from Source (C.1.4)

Enter the date specified in the withdrawn report.

[4] Base Date for Reporting (J2.2.1)

Enter the date when re-reporting is required.

[5] Comment on Base Date for Reporting (J2.2.2)

Describe the outline of the background leading to re-reporting.

[6] Sender’s (case) Safety Report Unique Identifier (C.1.1)

This should be a new safety report identifier. Do not use the identifier used in the withdrawal report.

[7] Worldwide Unique Case Identification Number (C.1.8.1)

In re-reporting after withdrawal of the report, use a new worldwide unique case identification number. Do not use the identifier used in the withdrawal report. However, if a case reported both in a post-marketing report and a clinical trial report is re-reported after one of the reports is withdrawn, use the worldwide unique case identifier remaining on the other report.

[8] Are there any other case identifiers in previous transmissions? (C.1.9.1)

Select "true."

[9] Source(s) of the Case Identifier (C.1.9.1.r.1)

The company's sender identifier should be provided.

[10] Case identifier(s) (C.1.9.1.r.2)

Enter the identification number (reporting category) and identification number (number) of the withdrawn report.

2. Handling of adverse reactions, etc. no longer subject to reporting

(1) Additional report of the case not subject to reporting

Only when all adverse reactions and infections correspond to any of the following [1] to [5] based on additional information, etc., the case may be considered not to be subject to reporting based on Article 228-20, Paragraph 1, Items 1 and 2 of the Regulation. However, if it is judged inappropriate to exclude it from reporting based on inquiries, etc. from PMDA about the contents not subject to reporting, the case should be handled by making an additional report.

When reporting the case as the case not subject to reporting, make an additional report on the case not subject to reporting by entering additional information along with "elements that must be described in the completion report" (essential elements), entering "Completed = Completed" in "Complete / Incomplete Category (J2.7.1)" and "1 = Not subject to reporting" in "Flag for Not Subject to Reporting (J2.8.1)," and describing the reason corresponding to "Reason for Not Subject to Reporting (J2.8.2)." Do not enter anything in "Report Nullification / Amendment (C.1.11.1)" and "Reason for Nullification / Amendment (C.1.11.2)." Refer to "3. Examples of description of adverse reactions, etc. not subject to reporting" for detailed method of description.

[1] When the causal relationship between the suspected in-house drug and the adverse reaction/infection is ruled out by the reporter and the sender

[2] When the adverse reaction is found to be non-serious

[3] When the adverse reaction is found to be a known reaction in an overseas case

[4] When the infection is found to be a known non-serious infection in a case in Japan

[5] When the infection is found to be a non-serious infection in an overseas case

(2) Points to consider for "Reaction(s) / Event(s) (E.i)," etc.

- A. If the above 2. (1) applies, all events entered in the previous report shall be entered in accordance with (1) or (2) of "3. Examples of description of adverse reactions, etc. not subject to reporting." If names of adverse reactions/infections in the previous report are changed, it is acceptable to correct them in an additional report.
- B. If some adverse reactions/infections correspond to [1] to [5] in 2. (1) above based

on additional information, etc., enter these events in accordance with (3) or (4) of “3. Examples of description of adverse reactions, etc. not subject to reporting.”

- C. In cases in Japan, unknown adverse reactions that are changed from serious to non-serious shall be reported based on Article 228-20, Paragraph 3, (b) of the Regulation.
- (3) Points to consider for “Assessment of Relatedness of Drug to Reaction(s) / Event(s) (G.k.9.i.2.r),” etc.
- A. Even if all the reported adverse reactions/infections are no longer subject to reporting according to the above 2. (1) [1], enter the contents of the previous report (“1 = Suspect” or “3 = Interacting” for suspected drugs) in “Characterisation of Drug Role (G.k.1).” In addition, for all adverse reactions/infections entered in the previous report, the reporter’s and sender’s assessments should be entered in “Assessment of Relatedness of Drug to Reaction(s) / Event(s) (G.k.9.i.2.r)” in accordance with (1) in “3. Examples of description of adverse reactions, etc. not subject to reporting.”
- B. If some adverse reactions/infections correspond to [1] in 2. (1) above based on additional information, etc., remove these reactions/infections or state that there is no causal relationship in “G.k.9.i.2.r” in accordance with (3) of “3. Examples of description of adverse reactions, etc. not subject to reporting” in the additional report.
- C. The following terms may be used to describe the absence of a causal relationship for each event.

G.k.9.i.2.r.1 (Source of assessment)		G.k.9.i.2.r.3	
In the case of reporter	In the case of sender	(Result of assessment)	
Terms starting with “reporter”	Terms starting with “sender”	No causal relationship	NO*
PRIMARY SOURCE REPORTER	Terms starting with “company”	Not related to causal relationship	NOT RELATED*
		Unrelated	UNRELATED*
INITIAL REPORTER	Terms starting with “foreign company”	Negative	NEGATIVE*
		Definitely not	DEFINITELY NOT*
		No	No
		MANUFACTURER COMPANY	Not related
		Can be denied	Unrelated
		Negative	Negative
		Definitely not	Definitely Not
			*: All letters can be lower case.

- D. In an additional report that the case is not subject to reporting, even if there is no causal relationship between the previously reported adverse reactions/infections and the test drug (suspected drug) concerned, etc., the content that was previously reported (“1 = suspected” or “3 = interacting” for the test drug) should be entered

in “G.k.1 Characterisation of Drug Role.”

3. Examples of description of adverse reactions, etc. not subject to reporting  
(Examples of events)

A = Unknown/serious adverse reaction

B = Unknown/non-serious adverse reaction

C = Known/serious adverse reaction

D = Known/non-serious adverse reaction

E = Serious adverse event for which a causal relationship with the drug was ruled out by the reporting physician and the reporting company

\* The following description examples are shown on the assumption that B, D, and E are described although B, D, and E are events not subject to reporting of adverse reactions in Japan.

(1) When the causal relationship with all the reported adverse reactions is ruled out based on the additional information

	Report No. n	Report No. n + 1
E.i.2.1	A, B, C, D, E	A, B, C, D, E
G.k.9.i.2.r	A to D Causally related E Not causally related	A to E Not causally related
J2.7.1		Completed = Completed
J2.8.1		1 = Not subject to reporting
J2.8.2		Reason for not subject to reporting

(2) When all the reported adverse reactions turn out to be non-serious (except for E, which remains to be a serious adverse event) based on additional information

	Report No. n	Report No. n + 1
E.i.2.1	A, B, C, D, E	A, B, C, D, E
E.i.3.1	A Serious B Non-serious C Serious D Non-serious E Serious	A to D Non-serious E Serious
J2.7.1		Completed = Completed
J2.8.1		1 = Not subject to reporting
J2.8.2		Reason for not subject to reporting

(3) When the causal relationship with Event A is ruled out based on the additional information

	Report No. n	Report No. n + 1
E.i.2.1	A, B, C, D, E	A, B, C, D, E
G.k.9.i.2.r	A to D Causally related E Not causally related	A Not causally related B to D Causally related E Not causally related
H.4		That A was changed to Not causally related
J2.11		Description of change

(4) When there are multiple serious adverse reactions and Event A is changed to non-serious based on additional information

	Report No. n	Report No. n + 1
E.i.2.1	A, B, C, D, E	A, B, C, D, E
E.i.3.1	A Serious B Non-serious C Serious D Non-serious E Serious	A Non-serious B Non-serious C Serious D Non-serious E Serious
H.4		That A was changed to non-serious
J2.11		Description of change

## **Handling of Withdrawal of Reports and Adverse Reactions, etc. No Longer Subject to Reporting (clinical trials)**

### 1. Handling of withdrawal of reports

#### (1) Reports subject to withdrawal

In principle, reports can be withdrawn only when any of the following [1] to [4] is met. When withdrawing a report, select “1 = Nullification” for “Report Nullification / Amendment (C.1.11.1),” enter the applicable reason among the following [1] to [4] in “Reason for Nullification / Amendment (C.1.11.2),” and select “Completed = completed” for “Complete / Incomplete Category (J2.7.1).” Do not enter anything in “Flag for Not Subject to Reporting (J2.8.1)” and “Reason for Not Subject to Reporting (J2.8.2).”

[1] When the event is found to have occurred before administration of all study drugs (this does not apply for exacerbation)

[2] When the same information is found to have been reported in duplicate

[3] If the following elements are erroneously described:

“Identification Number (reporting category) (J2.1a)”

“Sender’s (case) Safety Report Unique Identifier (C.1.1)”

“Worldwide Unique Case Identification Number (C.1.8.1)”

“First Sender of This Case (C.1.8.2)”

[4] When there is no case or adverse reaction, etc.

**Blinded** cases shall be handled as follows.

[1] If the information on the assignment of the subject concerned cannot be revealed immediately for a compelling reason, the first report on the occurrence of the adverse reaction, etc. concerned should be made even under blinded condition, with the reason why unblinding cannot be performed. The reason why unblinding cannot be performed shall be provided in “Sender’s Comments (H.4).”

[2] If a case has been reported by listing only the investigational products as suspected drugs and entering the information on the test drug and the comparator, and it turns out after unblinding that the cause was the test drug, an additional report shall be made by deleting the descriptions under “Investigational Product Blinded (G.k.2.5)” and “Drug Identification (G.k.2)” for the comparator.

[3] If a case has been reported by listing only the investigational products as suspected drugs and entering the information on the test drug and the comparator, and it turns out after unblinding that the cause was the comparator, an additional report shall be made by deleting the descriptions under “Investigational Product Blinded (G.k.2.5)” and “Drug Identification (G.k.2)” for the test drug. If the control is placebo, the reporting company shall make a “withdrawal report” for stating this. The sponsor will provide the information to the company providing the comparator, and the company providing the comparator will report the case of the adverse reaction, etc. concerned as a “Post-marketing report of adverse reactions, etc.” The adverse reactions are not regarded as “expected” in terms of the test drug, based on the reports of adverse reactions, etc. to

the comparator.

(2) Re-reporting after withdrawal of the report

If any additional information on the case concerned is obtained after withdrawing the report and re-reporting is required, the initial report (first report) shall be prepared with attention paid to the following points.

[1] Identification Number (reporting category) (J2.1a)

Enter the applicable reporting category.

[2] Identification number (number) (J2.1)

Leave it blank.

[3] Date Report Was First Received from Source (C.1.4)

Enter the date specified in the withdrawn report.

[4] Base Date for Reporting (J2.2.1)

Enter the date when re-reporting is required.

[5] Comment on Base Date for Reporting (J2.2.2)

Describe the outline of the background leading to re-reporting.

[6] Sender's (case) Safety Report Unique Identifier (C.1.1)

This should be a new safety report identifier. Do not use the identifier used in the withdrawal report.

[7] Worldwide Unique Case Identification Number (C.1.8.1)

In re-reporting after withdrawal of the report, use a new worldwide unique case identification number. Do not use the identifier used in the withdrawal report. However, if a case reported both in a post-marketing report and a clinical trial report is re-reported after one of the reports is withdrawn, use the worldwide unique case identifier remaining on the other report.

[8] Are there any other case identifiers in previous transmissions? (C.1.9.1)

Select "true."

[9] Source(s) of the Case Identifier (C.1.9.1.r.1)

The company's sender identifier should be provided.

[10] Case Identifier(s) (C.1.9.1.r.2)

Enter the identification number (reporting category) and identification number (number) of the withdrawn report.

2. Handling of adverse reactions, etc. no longer subject to reporting

(1) Additional report of the case not subject to reporting

If all adverse reactions/infections correspond to any of the following [1] to [3] based on additional information, etc. and the case is no longer subject to reporting based on Article 273, Paragraph 1 or 2 of the Regulation, enter the additional information together with the "elements that must be described in the completion report" (essential elements), enter "Completed = Completed" in "Complete / Incomplete Category (J2.7.1)" and "1 = Not subject to reporting" in "Flag for Not Subject to Reporting (J2.8.1)," and describe the reason corresponding to "Reason for Not Subject to Reporting (J2.8.2)." Do not enter anything in "Report Nullification / Amendment (C.1.11.1)" and "Reason for Nullification / Amendment (C.1.11.2)." Refer to "3. Examples of description of adverse reactions, etc. not subject to reporting" for detailed method of description.

[1] When the causal relationship between all the study drugs subject to reporting and the adverse reaction/infection is ruled out by the reporter or the sender

[2] When the adverse reaction is found to be non-serious

[3] When the adverse reaction/infection turns out to be a known/serious (other than death or life-threatening) adverse reaction/infection

- (2). Points to consider for “Reaction(s) / Event(s) (E.i),” etc.
- A. If the above 2. (1) is met, all events entered in the previous report shall be entered in accordance with (1), (2), or (3) of “3. Examples of description of adverse reactions, etc. not subject to reporting.” If names of adverse reactions/infections in the previous report are changed, it is acceptable to correct them in an additional report.
- B. If some adverse reactions/infections correspond to [1] to [3] in 2. (1) above based on additional information, etc., enter these events in accordance with (4) or (5) of “3. Examples of description of adverse reactions, etc. not subject to reporting.”
- (3) Points to consider for “Assessment of Relatedness of Drug to Reaction(s) / Event(s) (G.k.9.i.2.r),” etc.
- A. Even if all the reported adverse reactions/infections are no longer subject to reporting according to the above 2. (1) [1], enter the contents of the previous report (“1 = Suspect” or “3 = Interacting” for suspected drugs) in “Characterisation of Drug Role (G.k.1).” In addition, for all adverse reactions/infections entered in the previous report, the reporting physician’s and reporting company’s assessments should be entered in “Assessment of Relatedness of Drug to Reaction(s) / Event(s) (G.k.9.i.2.r)” in accordance with (1) in “3. Examples of description of adverse reactions, etc. not subject to reporting.”
- B. If some adverse reactions/infections correspond to [1] in 2. (1) above based on additional information, etc., remove these reactions/infections or describe that there is no causal relationship in “G.k.9.i.2.r” in accordance with (4) of “3. Examples of description of adverse reactions, etc. not subject to reporting” in the additional report.
- C. The following terms may be used to describe the absence of a causal relationship for each event.

G.k.9.i.2.r.1 (Source of assessment)		G.k.9.i.2.r.3 (Result of assessment)	
In case of reporter	In case of sender		
Terms starting with “reporter”	Terms starting with “sender”	No causal relationship absent	NO*
		Not related to causal relationship	NOT RELATED*
PRIMARY SOURCE REPORTER	Terms starting with “company”	Unrelated	UNRELATED*
INITIAL REPORTER	Terms starting with “foreign company”	Negative	NEGATIVE*
	MANUFACTURER COMPANY	Definitely not	DEFINITELY NOT*
		No	No
		Not related	Not Related
		Can be denied	Unrelated
		Negative	Negative
		Definitely not	Definitely Not
			*: All letters can be lower case.

- D. In an additional report that the case concerned is not subject to reporting, even if there is no causal relationship between the previously reported adverse reactions/infections and the study drug (suspected drug) concerned, the content that was previously reported (“1 = suspected” or “3 = interacting” for the study drug) should be entered in “G.k.1 Characterisation of Drug role.”

3. Examples of description of adverse reactions, etc. not subject to reporting  
(Examples of events)

A = Unknown/serious (other than death or life-threatening) adverse reaction

B = Unknown/non-serious adverse reaction

C = Known/serious (other than death or life-threatening) adverse reaction

D = Known/non-serious adverse reaction

E = Serious adverse event for which a causal relationship with the drug was ruled out by the reporting physician and the reporting company

\* The following examples of description are shown on the assumption that B, D, and E are described although B, D, and E are events not subject to reporting.

- (1) When the causal relationship with all the reported adverse reactions is ruled out based on the additional information

	Report No. n	Report No. n + 1
E.i.2.1	A, B, C, D, E	A, B, C, D, E
G.k.9.i.2.r	A to D Causally related E Not causally related	A to E Not causally related
J2.7.1		Completed = Completed
J2.8.1		1 = Not subject to reporting
J2.8.2		Reason for not subject to reporting

- (2) When all the reported adverse reactions turn out to be non-serious (except for E, which remains to be a serious adverse event) based on additional information

	Report No. n	Report No. n + 1
E.i.2.1	A, B, C, D, E	A, B, C, D, E
E.i.3.1	A Serious B Non-serious C Serious D Non-serious E Serious	A to D Non-serious E Serious
J2.7.1		Completed = Completed
J2.8.1		1 = Not subject to reporting
J2.8.2		Reason for not subject to reporting

(3) When Event A is changed to a known event, the causal relationship with Event C is ruled out, and no events are subject to reporting based on the additional information. If multiple suspected drugs are subject to reporting, leave J2.14.i blank and enter the information on unknown/known for all suspected drugs subject to reporting in J2.11.

	Report No. n	Report No. n + 1
E.i.2.1	A, B, C, D, E	A, B, C, D, E
G.k.9.i.2.r	A to D Causally related E Not causally related	A, B, D Causally related C, E Not causally related
J2.7.1		Completed = Completed
J2.8.1		1 = Not subject to reporting
J2.8.2		Reason for not subject to reporting
J2.14.i	A Unknown B Unknown C Known D Known E Unknown	A Known B Unknown C Known D Known E Unknown

(4) When the causal relationship with Event A is ruled out based on the additional information

	Report No. n	Report No. n + 1
E.i.2.1	A, B, C, D, E	A, B, C, D, E
G.k.9.i.2.r	A to D Causally related E Not causally related	A Not causally related B to D Causally related E Not causally related
H.4		That the causal relationship with Event A is ruled out
J2.11		Description of change

(5) When there are multiple serious adverse reactions and a part of events (Event A) is changed to non-serious based on additional information

	Report No. n	Report No. n + 1
E.i.2.1	A, B, C, D, E	A, B, C, D, E
E.i.3.1	A Serious B Non-serious C Serious D Non-serious E Serious	A Non-serious B Non-serious C Serious D Non-serious E Serious
H.4		That A was changed to non-serious
J2.11		Description of change

**Handling of Withdrawal of Reports and Adverse Reactions, etc. No Longer Subject to Reporting (reports of adverse reactions to quasi-drugs, etc.)**

1. Handling of withdrawal of reports

(1) Reports subject to withdrawal

In principle, reports can be withdrawn only when any of the following [1] to [5] is met. However, if the withdrawal is judged to be inappropriate based on the inquiries, etc. about the contents of withdrawal from PMDA, actions such as re-reporting shall be taken.

When withdrawing a report, select “1 = Nullification” for “Report Nullification / Amendment (C.1.11.1),” enter the applicable reason among the following [1] to [5] in “Reason for Nullification / Amendment (C.1.11.2),” and select “Completed = completed” for “Complete / Incomplete Category (J2.7.1).” Do not enter anything in “Flag for Not Subject to Reporting (J2.8.1)” and “Reason for Not Subject to Reporting (J2.8.2).”

[1] When it is found that no in-house product was used

[2] When the adverse reaction is found to have occurred before the use of the in-house product (this does not apply for exacerbation)

[3] When the same information is found to have been reported in duplicate

[4] If the following elements are erroneously described:

“Identification Number (reporting category) (J2.1a)”

“Sender’s (case) Safety Report Unique Identifier (C.1.1)”

“Worldwide Unique Case Identification Number (C.1.8.1)”

“First Sender of This Case (C.1.8.2)”

[5] When there is no case

(2) Re-reporting after withdrawal of the report

If any additional information on the case concerned is obtained after withdrawing the report and re-reporting is required, the initial report (first report) shall be prepared with attention paid to the following points.

[1] Identification Number (reporting category) (J2.1a)

Enter the applicable reporting category.

[2] Identification Number (number) (J2.1b)

Leave it blank.

[3] Other Reference Matters, etc. (J2.11)

Enter the identification number of the withdrawn report.

[4] Date Report was First Received from Source (C.1.4)

Enter the date specified in the withdrawn report.

[5] Base Date for Reporting (J2.2.1)

Enter the date when re-reporting is required.

[6] Sender’s (case) Safety Report Unique Identifier (C.1.1)

This should be a new safety report identifier. Do not use the identifier used in the withdrawal report.

[7] Worldwide Unique Case Identification Number (C.1.8.1)

In re-reporting after withdrawal of the report, use a new worldwide unique case

identification number. Do not use the identifier used in the withdrawal report.

[8] Sender's Comments (H.4)

Describe the outline of the background leading to re-reporting.

2. Handling of adverse reactions, etc. no longer subject to reporting

(1) When all adverse reactions are no longer subject to reporting

Only when all adverse reactions correspond to either [1] or [2] below based on additional information, etc., the case may be considered not to be subject to reporting based on Article 228-20, Paragraph 5, Items 1 and 2 (a) of Regulation. However, if it is judged inappropriate to exclude it from reporting based on the inquiries, etc. from PMDA about the contents not subject to reporting, the case should be handled by making an additional report.

When reporting the case as the case not subject to reporting, make an additional report on the case not subject to reporting by entering additional information along with "elements that must be described in the completion report" (essential elements), entering "Completed = Completed" in "Complete / Incomplete Category (J2.7.1)" and "1 = Not subject to reporting" in "Flag for Not Subject to Reporting (J2.8.1)," and describing the reason corresponding to "Reason for Not Subject to Reporting (J2.8.2)." Do not enter anything in "Report Nullification / Amendment (C.1.11.1)" and "Reason for Nullification / Amendment (C.1.11.2)."

[1] When the causal relationship between all the adverse reactions and the suspected in-house product is ruled out by the reporter and the sender

[2] When all the adverse reactions are found to be non-serious. In other words, when there is no applicable reaction in "Seriousness, etc. (J2.26.i)."

(2) When some adverse reactions are no longer subject to reporting

If some adverse reactions are found to correspond to [1] or [2] in 2. (1) above based on additional information, etc., make an additional report by deleting the information on these adverse reactions. In this case, do not enter anything in J2.8.1 and J2.8.2. Describe the background, rationale, etc. for the change in the evaluation of causal relationship or seriousness in H.4.

## Immediate Reports

### 1. Immediate reports (post-marketing reports of adverse reactions, etc.)

#### (1) Means of sending immediate reports

In the case of immediate reporting, any of the following means can be used for transmission. Select appropriate measures depending on the situation. However, if information necessary for electronic reporting cannot be obtained promptly, send the report by fax: be careful not to delay the immediate report.

Note that reports of adverse reactions to quasi-drugs, etc. can only be sent by fax.

FAX	Electronic reporting
<ul style="list-style-type: none"> <li>• To be used when information necessary for electronic reporting cannot be obtained promptly and in other cases.</li> <li>• Apart from immediate reporting by fax, the usual post-marketing report of adverse drug reactions, etc. needs to be made by electronic reporting, reporting by CD, etc., or paper-based reporting within the reporting deadline.</li> </ul>	<ul style="list-style-type: none"> <li>• To be used when information necessary for electronic reporting has been obtained promptly.</li> <li>• Since the immediate report also serves as the usual post-marketing report of adverse reactions, etc., it is not necessary to separately make a usual post-marketing report of adverse reactions, etc. (If additional information is obtained, make an additional report.)</li> </ul>

#### (2) How to use Immediate Report Flag (J2.3)

- Use J2.3 only for immediate reports made by electronic reporting. Leave this element blank if an immediate report is submitted by fax.
- Enter “1 = Immediate report” only when the report is an immediate report. Leave this element blank for an additional report after an immediate report made by electronic reporting or for a usual post-marketing report of adverse reactions, etc. after an immediate report made by fax.
- For a case that has already been reported in a post-marketing report of adverse reactions, etc., if the case is found to correspond to immediate reporting based on additional information, the additional report by electronic reporting can be made as an immediate report by using J2.3.

#### (3) Points to consider when sending an immediate report by fax

If sending an immediate report by fax, clearly state “Report by fax/To Office of Pharmacovigilance I or Office of Pharmacovigilance II (Office of Manufacturing Quality and Vigilance for Medical Devices for in vitro diagnostics)” in Attached Form 1 or 5 of Post-marketing Director-General Notification (or Attached Form 1 for quasi-drugs, etc. in cases of reports of adverse reactions to quasi-drugs, etc.) and send the report with as much information as the marketing authorization holder is aware of at the time of reporting. It is acceptable to submit it to the PMDA reception instead of sending it by fax.

## 2. Immediate reports (reports of adverse reactions, etc. in clinical trials)

In case of emergency that requires discontinuation of the clinical trial, the initial report should be made by e-mail, etc. after contacting the Review Planning Division, Office of Review Management, PMDA by phone in advance. In this case, the date on which the e-mail, etc. is received is regarded as the date of the report. However, separately from the immediate report by e-mail, etc. (report of adverse reactions, etc. in clinical trials), a usual report of adverse reactions, etc. in clinical trials should be made by electronic reporting, etc. by the reporting deadline.

In reporting by e-mail, etc., the currently available information should be described in the applicable items in the attached form of the Clinical Trial Director-General Notification. When reporting by e-mail, the subject line and file name should be “Immediate report (report of adverse reactions, etc. in clinical trials)\_Test substance identification code of the main test drug\_Reporter name,” and the report shall be sent to [tiken-toiawase@pmda.go.jp](mailto:tiken-toiawase@pmda.go.jp). When reporting by fax, clearly state “Immediate report/To Review Planning Division, Office of Review Management” in Attached Forms 1, 3, and 5 of the Clinical Trial Director-General Notification and send them by fax to 03-3506-9443. Note that immediate reports (reports of adverse reaction, etc. in clinical trials) by e-mail, etc. should not be counted when counting the number of reports to PMDA.

Only when the information on elements essential for electronic reporting is available at the time when immediate reporting becomes necessary, it is acceptable to make electronic reporting instead of sending e-mails, etc. after contacting PDMA by phone. Since this immediate report is handled as a usual report on adverse reactions, etc. in clinical trials, when additional information is obtained, it should be handled as an additional report. Do not use Immediate Report Flag (J2.3) for immediate reports (reports of adverse reaction, etc. in clinical trials).

## Actions To Be Taken at the Time of Succession, etc. in Adverse Reaction Reports

For handling and procedures for additional reports after succession of drugs or quasi-drugs, etc. or merger, etc. of companies in post-marketing reports of adverse reactions, etc. and additional reports after the change of the sponsor in reports of adverse reactions, etc. in clinical trials, attention shall be paid to the following matters.

### 1. Handling of additional reports

When the succeeding company makes, after succession, an additional report of a case reported in a report of adverse reactions, etc. of drugs or quasi-drugs, etc. made by the original company, or when the company established after merger makes an additional report of a case reported in a report of adverse reactions, etc. made before the merger, follow the procedures in (1) and (3) below. When the new sponsor makes an additional report of adverse reactions, etc. made by the original sponsor, follow the procedures in (2) and (3) below.

- (1) Documents to be submitted before the additional report for a post-marketing report of adverse reactions, etc.

In succession of drugs or quasi-drugs, etc., registration shall be made using Appendix 1 (1) “Registration Form for Succession, etc.” before the succeeding company makes an additional report. In the case of a merger, Appendix 1 (1) shall be submitted before one representative company makes an additional report. If a new sender identifier is used after merger, an application for change of the sender identifier should be made using Appendix 2, “Sender Identifier Application Form.” If an additional report is made without submission of these documents, it will not be received; therefore, be sure to submit them in advance.

- (2) Documents to be submitted before the additional report for a report of adverse reactions, etc. in clinical trials

If the sponsor is changed, registration shall be made using Appendix 1 (2) “Registration Form for Succession (change of sponsor)” before the new company makes an additional report. If an additional report is made without registration, it will not be received; therefore be sure to submit them in advance.

- (3) E2B data elements description guideline

The E2B data elements listed in the table below should be described in accordance with the guidelines provided in the table.

E2B data element number	E2B data element name	Description guideline
N.2.r.2	Message Sender Identifier	Enter the sender identifier after succession/merger (after change in the case of clinical trials).
J2.1a	Identification Number (reporting category)	The same reporting category as that of the previous report should be used.
J2.1b	Identification Number	The same number as that of the previous report

	(number)	should be used.
N.2.r.1 C.1.1	Message Identifier Safety Report Identifier	Enter the new safety report identifier.
C.1.8.1	Worldwide Unique Case Identification Number	The same identifier as the previous report should be used.
C.1.8.2	First Sender of This Case	The same sender as that of the previous report should be selected.
C.1.9.1.r.1	Source(s) of the Case Identifier	Enter the Message Sender Identifier (N.2.r.2) of the previous report.
C.1.9.1.r.2	Case Identifier(s)	Enter the Safety Report Identifier (C.1.1) of the previous report.

## 2. Documents to be submitted at the time of merger

If there is any change in the company's main e-mail address or the person in charge of reports of adverse reactions, etc. at the time of merger, submit Appendix 3, "Registration Form for Companies Reporting Adverse Reactions, etc. and Persons in Charge," or register the change on the screen for registration of information on persons in charge at companies at the PMDA ICSR reporting site (hereinafter referred to as the "reporting site").

### **Documents To Be Attached to Reports of Adverse Reactions, etc.**

#### 1. Handling of reports with submission data in ICSR files

If there are any data to be attached to a report of adverse reactions, etc., it is desirable to include the submission data in the ICSR file in which the matters specified in the attached form are described. When the data cannot be attached to the ICSR file for reporting, submit them in accordance with “2. Handling of submission data to be sent at reception or via postal mail, etc.”

- (1) As shown in the E2B (R3) Implementation Guide Notification, there are two E2B data elements to which data are to be attached. Select one of them depending on the contents of submission data. When attaching data other than references such as ECG and X-ray, enter “true” in “Are Additional Documents Available? (C.1.6.1),” enter necessary information in “Documents Held by Sender (C.1.6.1.r.1),” and attach the data to “Included Documents (C.1.6.1.r.2).” When attaching references, enter necessary information in “Literature Reference(s) (C.4.r.1)” and attach the literature in “Included Documents (C.4.r.2).”
- (2) When making an additional report, keep the titles, etc. of the data attached to the previous report (do not delete them), but do not attach the data themselves again. If there are any data to be newly attached, enter the titles, etc. of the data in addition to the titles, etc. of the original submission data, and attach the data.
- (3) If the submission data cannot be obtained by the time of reporting, it is acceptable to enter necessary information in “Documents Held by Sender (C.1.6.1.r.1)” or “Literature Reference(s) (C.4.r.1)” and make a report without attaching the data. In this case, state in “Other Reference Matters, etc. (J2.11)” that the data will be sent at a later date.
  - A. After the submission data are obtained, if the information on the case has not changed at all and only the submission data are added to the ICSR file, make an additional report by selecting “2 = Amendment” in “Report Nullification / Amendment (C.1.11.1).”
  - B. If there is any additional information on the case when the data are obtained and the information on the case is to be changed, do not enter anything in “Report Nullification / Amendment (C.1.11.1),” but enter other necessary information to make a usual additional report.
- (4) File format, etc.
  - A. The following file formats can be submitted.  
PDF, JPG, JPEG, BMP, PNG, GIF, TIF, TIFF, RTF, TXT, MS-EXCEL, MS-WORD, HTML, DICOM, XML  
Submission of ZIP files is not allowed.

- B. DF or GZIP should be used as a compression algorithm.
  - C. The encoding method shall be BASE64.
- (5) If the submission data exceed the maximum capacity, extract only the parts related to the reported contents. If it is still difficult to fit the information in the ICSR file, submission of CD, etc. or paper-based media at the reception or by postal mail, etc. is acceptable, instead of submitting electronically. In this case, enter necessary information in “Documents Held by Sender (C.1.6.1.r.1)” or “Literature Reference(s) (C.4.r.1),” and state in “Other Reference Matters, etc. (J2.11)” that the data will be submitted at the reception or by postal mail, etc.
  - (6) The personal information of patients, etc. included in the submission data should be masked beforehand as needed.
2. Handling of submission data to be sent at reception or via postal mail, etc.
    - (1) Since the submission data are a part of the report, it is desirable to submit them at the same time as the report of adverse reactions, etc. When sending the submission data at a later date for unavoidable reasons, submit them promptly together with Appendix 4, “Slip for Mailing Reports of Adverse Reactions, etc.,” which includes necessary information so that there may be no significant delay from the date of reporting of the adverse reactions, etc.
    - (2) When sending the submission data in CD, etc., see “5. Preparation of CD, etc. for Submission Data” for the method for preparing the CD, etc. Reporters’ cooperation in sending the submission data not in paper-based media, but in ICSR file or CD, etc. is appreciated.
    - (3) When sending the submission data in paper-based media, pay attention to the following points.
      - A. When sending the data before assignment of an identification number, provide a reference number and drug name, etc. (the test substance identification code of the main test drug in the case of reports of adverse reactions, etc. in clinical trials, and the product name in the case of reports of adverse reactions to quasi-drugs, etc.) in the upper right corner of the data concerned.
      - B. When sending the submission data after assignment of an identification number, provide the identification number of the report to which the data will be attached, number of reports, and drug name, etc. (the test substance identification code of the main test drug in the case of reports of adverse reactions, etc. in clinical trials, and the product name in the case of reports of adverse reactions to quasi-drugs, etc.) in the upper right corner of the data concerned.
  3. Handling of package inserts, etc. of drugs or quasi-drugs, etc. related to post-marketing reports of adverse reactions, etc.
    - (1) For prescription drugs and drugs requiring guidance, new submission is not required. However, if requested by Office of Pharmacovigilance I or Office of Pharmacovigilance II (or Office of Manufacturing Quality and Vigilance for Medical Devices for in vitro diagnostics), PMDA, submit them promptly.
    - (2) For over-the-counter drugs (including in vitro diagnostics that are over-the-counter drugs), submit the package insert of the suspected in-house drug in the reports of adverse reactions in Japan related to 15-day reporting, as well as in all infection

- reports, research reports, and foreign corrective action reports.
- (3) For quasi-drugs/cosmetics, regardless of the reporting category, submit the information provided on the immediate container, etc. and in the package insert, etc. of the suspected in-house drug.
  - (4) When submitting the package insert, it is desirable to include the package insert, etc. in the ICSR file in the same manner as sending of the submission data. When reporting by including the package insert, etc. in the ICSR file, submit the report according to “1. Handling of reports with submission data in ICSR files.” When the package insert, etc. cannot be included in the ICSR file for reporting, submit it in accordance with “2. Handling of submission data to be sent at reception or via postal mail, etc.”
4. Preparation of CD, etc. for submission data
- (1) Follow the rules below for preparation of CD, etc. for submission data.
    - A. File name and content

The format should be as follows.  
T-Reporting category (2 digits)-Identification number (8 digits)-Number of reports (2 digits)-Branch number (3 digits).xxx (extension) (half-width alphanumeric characters)  
Example) T-AB-16500001-02-001.pdf  
File format: File formats shown in 1. (5)  
Enter the number of reports shown in the ACK message for the report to which submission data are to be attached, and enter the serial number of the submission data assigned for each number of reports for the branch number.
    - B. Format of electronic media
      - (a) CD-R (ROM)  
Format: ISO 9660 standard level 3 and Joliet, Romeo  
Size: 650 MB or 700 MB
      - (b) DVD-R (ROM)  
Format: ISO 9660 Universal Disk Format (UDF 2.00)  
Size: 4.7 GB
    - C. Points to consider
      - (a) The file formats of the submission data that can be sent should be the same as the file formats that can be attached to the electronic report.
      - (b) Multiple submission data files may be saved in one CD, etc. The submission data files associated with multiple identification numbers may also be saved in one CD, etc.
      - (c) Do not compress submission data files using zip format, etc. when saving them on CDs, etc.
      - (d) On CD, etc. containing submission data files, be sure to place the label showing the identification number, drug name, etc. (the test substance identification code in the case of reports of adverse reactions, etc. in clinical trials, and product name in the case of reports of adverse reactions to quasi-drugs, etc.), and the name of the submission data file.

### Handling of E2B (R2) Reports and E2B (R3) Reports

The points to consider when switching from reports according to the E2B (R2) Guideline (hereinafter referred to as the “R2 reports”) to reports according to the E2B (R3) Guideline (hereinafter referred to as the “R3 reports”) are shown below.

1. Additional reports by the R3 reports for the R2 reports
  - (1) For the elements for which different coding systems are used in the E2B (R2) and the E2B (R3), the data should be newly coded with the coding system of the R3 reports at the time of switching to the R3 reports.

Example)

Data element name	Data element number	R2 reports	R3 reports
Identification number (reporting category)	R2:J.4a/R3:J2.1a	B	AB
Complete/incomplete category	R2:J.6/R3:J2.7.1	1 (= not completed)	active (= not completed)

- (2) The elements that are not changed at the time of the additional report should not be changed, in principle, at the time of making an additional report by switching to the R3 report.
- (3) For elements other than (1) and (2) above, read them referring to “E2B (R2) and E2B (R3) Compatibility Recommendations” in Attachment 2 of the E2B (R3) Implementation Guide Notification and update the descriptions as needed to make an R3 report.

## Reception of Reports of Adverse Reactions, etc.

### 1. Reporting method

PMDA accepts post-marketing reports of adverse reactions, etc. (excluding reports of adverse reactions to quasi-drugs, etc.) and reports of adverse reactions, etc. in clinical trials by electronic reporting, reporting by CD, etc., or paper-based reporting, but electronic reporting is preferable. For electronic reporting, there are a method of reporting by the AS1 specifications (SMTP) or AS2 specifications (HTTPS) using the EDI tool and another method by uploading via the reporting site.

PMDA accepts reports of adverse reactions to quasi-drugs, etc. by electronic reporting, reporting by e-mail, or paper-based reporting, but electronic reporting or reporting by e-mail is preferable.

Reports by CD, etc. and paper-based reports are received at the reception and may also be submitted by postal mail, etc.

Regardless of the reporting method, it is necessary to prepare an ICSR file describing the matters to be reported. For technical information on ICSR file preparation, see Attachment 10.

### 2. Procedures before submission of reports

(1) Marketing authorization holders and sponsors of clinical trials who make electronic reports, reports by CD, etc., paper-based reports, or reports by e-mail shall meet both of the following requirements, A and B.

A. The sender identifier has been registered using Appendix 2, "Sender Identifier Application Form."

B. Appendix 3, "Registration Form for Companies Reporting Adverse Reactions, etc. and Persons in Charge," has been submitted or registration on the screen for registration of information on persons in charge at companies of the reporting site has been completed.

(2) Marketing authorization holders and sponsors of clinical trials who make electronic reports shall meet all the requirements in the following A or B in addition to (1).

A. When reporting using the EDI tool

(a) Appendix 5, "Prior Confirmation Sheet for Electronic Reporting," has been submitted.

(b) Appendix 6, "Registration Form for Required Items for Electronic Reporting," has been submitted.

(c) Connection with the management system for information on adverse drug reactions (hereinafter referred to as "the system") has been confirmed. Marketing authorization holders and sponsors who wishes to undergo confirmation of the connection shall apply using Appendix 7, "Application Form for Confirmation of Connection."

(d) Those who wish to use the reporting site shall submit Appendix 8, "Application Form for Use of PMDA ICSR Reporting Site."

B. When reporting by uploading at the reporting site

(a) Appendix 8 has been submitted, the account has been created, and the public key certificate has been registered.

(b) The R3 signature/encryption tool has been downloaded from the SKW site, and the public key certificate and private key certificate have been set.

(c) If an ICSR file is to be created using a tool provided by PMDA, the ICSR file creation tool or the ICSR file creation tool for quasi-drugs, etc. has been downloaded from the SKW site.

### 3. Initial reports and additional reports

#### (1) Initial reports

In the initial report (first report), enter information in accordance with the entry condition symbols shown in Appendices 1 and 2 of the 2020 E2B (R3) Two Director Notification. However, "Identification Number (number) (J2.1b)" can be left blank.

#### (2) Additional reports

Similarly to the initial report, enter information in the additional report (second or subsequent reports) in accordance with the entry condition symbols shown in Appendices 1 and 2 of the 2020 E2B (R3) Two Director Notification. Pay attention to the following points.

#### A. Identification Number (reporting category) (J2.1a), Identification Number (number) (J2.1b)

The identification number (reporting category) should be the same as that of the initial report. Enter the identification number (number) shown in "Local Report Number (ACK.B.r.2)" among the elements of the ACK message to the initial report.

#### B. Message Identifier (N.2.r.1)

Enter the same identifier as the Safety Report Identifier (C.1.1) of the report.

#### C. Message Sender Identifier (N.2.r.2)

Enter the same sender identifier as the initial report. If the sender identifier is to be changed because of succession of drugs, test drugs, or quasi-drugs, etc. or merger of companies, an additional report shall be made after registration in advance using Appendix 1 (1), "Registration Form for Succession, etc.," or Appendix 1 (2), "Registration Form for Succession (change of sponsor)." See Attachment 6 for details of succession, etc.

#### D. Sender's (case) Safety Report Unique Identifier (C.1.1)

Enter the same identifier as that of the initial report. However, changes of the sender identifier due to succession or merger and changes of the identifier due to changes of the country code are permitted.

#### E. Worldwide Unique Case Identification Number (C.1.8.1)

Enter the same identifier as that of the initial report.

### 4. Time when reports are received

#### (1) Electronic reporting

Reports can be received 24 hours, in principle. After receiving the report, PMDA will process the report as needed and send back the ACK file. However, the report received during the system maintenance period will be processed for receipt after completion of maintenance, and the ACK file will be sent.

The system maintenance period is usually from midnight to 6:00 a.m. on business days of PMDA and on weekends and holidays. However, maintenance may be performed at other times as needed.

- (2) Receipt of reports by CD, etc. or paper-based reports at reception

Reports are received from 9:30 a.m. to 5:00 p.m. on business days of PMDA, in principle. If the arrival is expected to be after 5:00 p.m. due to unavoidable reasons such as traffic conditions, reports are received until 5:45 p.m. only if Information Management Section, Office of Informatics and Management for Safety, PMDA is notified of this in advance.
  - (3) Reporting by e-mail

Reports can be received 24 hours, in principle. PMDA will process e-mails received from 9:30 a.m. to 5:00 p.m. on business days as those received on the day. E-mails received after 5:00 p.m. are regarded as those received on the next PMDA business day.
5. Date of receipt/date of transmission
- The date of receipt and the date of transmission in each reporting method are as follows. However, if PMDA instructs the reporter to re-submit at the time of the receipt for correction of inadequacies, etc., the date on which PMDA receives the re-submitted report will be regarded as the date of receipt of the report.
- (1) Electronic reporting

The report is considered to have been made at the time of registration with PMDA's electronic data processing system, and the date is shown in an ACK message element, "Acknowledgement Date of Batch Transmission (ACK.M.4)." Reports received by 23:59 will be regarded as those received on the day. For reports sent during the system maintenance at night, etc., note that the date and time of recording of the report after the end of maintenance will be regarded as the date of receipt. The "Date of Batch Transmission (N.1.5)" shall be the date and time when the report was electronically transmitted.
  - (2) Reporting by CD, etc.

The report is considered to have been made at the time of registration with PMDA's electronic data processing system, and the date is shown in an ACK message element, ACK.M.4. N.1.5 shall be the date of submission to the reception or the date of shipment if the report is sent by postal mail, etc.
  - (3) Paper-based reporting

The report received date will be when the report is submitted at the reception of PMDA, or when the report via postal mail, etc. is received by PMDA. The identification number is issued not at the time of the receipt of paper-based reports, but when the ICSR file is registered to the electronic data processing system of PMDA. N.1.5 shall be the date of submission to the reception or the date of shipment if the report is sent by postal mail, etc.
  - (4) Reporting by e-mail

The report is considered to have been made at the time of registration with PMDA's electronic data processing system, and the date is shown in an ACK message element, ACK.M.4. N.1.5 shall be the date of e-mail transmission. Note that if the submission of Attached Form 1 for quasi-drugs, etc. (original) is not confirmed at a later date, the receipt shall be retracted.
6. Number of copies of reporting documents and submission data to be submitted, method of submission, etc.

Note that the number of copies of reporting documents, submission data, etc. to be submitted, method of submission, etc. are different in electronic reporting, reporting by CD, etc., paper-based reporting, and reporting by e-mail. For documents, use Japan Industrial Standards A4 paper and print on one side. For preparation of the labels for CD, etc., follow the method described on the SKW site shown in Note 3. For documents to be attached to reports, see Attachment 7.

- (1) Electronic reporting (excluding reports of adverse reactions to quasi-drugs, etc.)
  - A. Items to be submitted
    - (a) ICSR file
    - (b) If submission data are sent by postal mail, etc. separately from the ICSR file, CD, etc. containing submission data or 1 copy of submission data in paper-based media
    - (c) If submission of the package insert is required based on 3 of Attachment 7 in a post-marketing report of adverse reactions, etc. and the package insert is submitted separately from the ICSR file, CD, etc. containing the package insert as a PDF file or 1 copy of the package insert in paper-based media
    - (d) If (b) and (c) are submitted by postal mail, etc., 1 copy of Appendix 4, "Slip for Mailing Reports of Adverse Reactions, etc."

On the front of the envelope to be sent, write either "Post-marketing report of adverse reactions, etc." or "Report of adverse reactions, etc. in clinical trials" in red.

- (2) Reporting by CD, etc.
  - A. Items to be submitted
    - (a) CD, etc. containing the ICSR file
    - (b) A document describing necessary information (if wishing for return, submit one duplicate copy as well)
    - (c) If submission data are sent separately from the ICSR file, CD, etc. containing submission data or 2 copies of submission data in paper-based media
    - (d) If submission of the package insert is required based on 3 of Attachment 7 in a post-marketing report of adverse reactions, etc. and the package insert is submitted separately from the ICSR file, CD, etc. containing the package insert as a PDF file or 1 copy of the package insert in paper-based media
    - (e) If (a) to (d) are submitted by postal mail, etc., one each of Appendix 4, "Slip for Mailing Reports of Adverse Reactions, etc.," and stamped self-addressed envelope.

On the front of the envelope to be sent, write either "Post-marketing report of adverse reactions, etc." or "Report of adverse reactions, etc. in clinical trials" in red.

- B. A document describing necessary information

In addition to the name and address of the reporting company and the date of reporting shown in Post-marketing Director-General Notification and Clinical Trial Director-General Notification, the matters related to the following (a) to (j) shall be entered as other necessary information. This document should be prepared for each case, and the attached form should be used, in principle.

- (a) Identification number (excluding the first report)
- (b) Date on which first report was received
- (c) Whether it is a "15-day report" or a "30-day report" (whether it is a "7-day report" or a "15-day report" in the case of reports of adverse reactions, etc. in clinical trials)
- (d) Brand name (for reports of adverse reactions, etc. in clinical trials, "test substance identification code")

- (e) Generic name
  - (f) Sender's (case) safety report unique identifier
  - (g) Category of report (adverse reaction/infection) and in Japan/overseas
  - (h) Reporting category symbol
  - (i) Date of most recent information for this report
  - (j) The fact that the report is withdrawn (in the case of withdrawal reports)
- (3) Paper-based reporting (excluding reports of adverse reactions to quasi-drugs, etc.)
- If electronic reporting cannot be implemented temporarily because of system failure, etc. and paper-based reporting is performed instead, inform the Review Planning Division, Office of Review Management, PMDA of this circumstance at the time of paper-based reporting. After the ICSR file recorded in the CD, etc. submitted at the time of paper-based reporting is received and the system is normalized, the additional report should be made by electronic reporting.
- If a report in the attached form is accepted, but the contents of the ICSR file recorded in CD, etc. cannot be accepted, CD, etc. shall be re-submitted. When re-submitting CD, etc., enter the same date as that in the report in "Date Report Was First Received from Source (C.1.4)," "Date of Most Recent Information for This Report (C.1.5)," and "Base Date for Reporting (J2.2.1)," and state that the report has already been received and enter the report received date in "Comment on Base Date for Reporting (J2.2.2)."
- A. Items to be submitted
- (a) One copy of the report in the attached form (if the receipt stamp is desired, submit one duplicate copy)
  - (b) CD, etc. containing the ICSR file
  - (c) If submission data are sent separately from the ICSR file, CD, etc. containing submission data or one copy of submission data in paper-based media
  - (d) If submission of the package insert is required based on 3 of Attachment 7 in a post-marketing report of adverse reactions, etc. and the package insert is submitted separately from the ICSR file, CD, etc. containing the package insert as a PDF file or 1 copy of the package insert in paper-based media
  - (e) If (a) to (d) are submitted by postal mail, etc., one each of Appendix 4, "Slip for Mailing Reports of Adverse Reactions, etc.," and stamped self-addressed envelope.
- On the front of the envelope to be sent, write either "Post-marketing report of adverse reactions, etc." or "Report of adverse reactions, etc. in clinical trials" in red.
- (4) Electronic reporting (reports of adverse reactions to quasi-drugs, etc.)
- A. Items to be submitted
- (a) ICSR file
  - (b) CD, etc. or a copy of paper-based media including description such as information on an immediate container, separately from the ICSR file
  - (c) CD, etc. or a copy of paper-based media including description such as package insert
  - (d) If submission data are sent by postal mail, etc. separately from the ICSR file, CD, etc. containing submission data or 1 copy of submission data in paper-based media
  - (e) If (b) to (d) are submitted by postal mail, etc., 1 copy of Appendix 4, "Slip for Mailing Reports of Adverse Reactions, etc."
- (5) Reporting by e-mail
- The documents to be submitted shown in A. below shall be submitted directly to the

reception at PMDA or sent by postal mail, etc., and the ICSR file in B. shall be submitted to PMDA by e-mail.

- A. Documents to be submitted at PMDA reception or by postal mail, etc.
    - (a) Attached Form 1 for quasi-drugs, etc. including information to be reported (original): 1
    - (b) Copy of the information provided on the immediate container, etc.: 1
    - (c) Copy of the information included in the package insert, etc.: 1
    - (d) If submission data are to be sent separately from the ICSR file, CD, etc. containing submission data or one copy of submission data in paper-based media (If submission data are sent before the identification number is assigned to the initial report, submit them in paper-based media; after the identification number is given, the submission data file can be sent as an attachment to an e-mail)
    - (e) If (a) to (d) are submitted by postal mail, etc., one each of Appendix 4, "Slip for Mailing Reports of Adverse Reactions, etc.," and stamped self-addressed envelope
  - B. Documents to be submitted by e-mail
    - (a) ICSR file containing the matters listed in the attached forms for quasi-drugs, etc.
- (6) Paper-based reporting (reports of adverse reactions to quasi-drugs, etc.)

A. Items to be submitted

The documents to be submitted shown below shall be submitted directly to the reception at PMDA or sent by postal mail, etc.

- (a) Attached forms for quasi-drugs, etc.: 1
  - (b) Copy of the information provided on the immediate container, etc.: 1
  - (c) Copy of the information included in the package insert, etc.: 1
  - (d) Attached documents (to be submitted only when necessary): 1
  - (e) ICSR file containing the matters listed in the attached forms for quasi-drugs, etc.
  - (f) If (a) to (e) are submitted by postal mail, etc., one each of Appendix 4, "Slip for Mailing Reports of Adverse Reactions, etc.," and stamped self-addressed envelope
- B. Handling of a copy of description on immediate containers, etc. and description in package insert, etc.
- (a) Only the primary suspected product is subject to submission of these items, but these items regarding other suspected in-house products and concomitant suspected in-house products should be submitted promptly if requested by PMDA.
  - (b) When the primary suspected product is reported using a series name, it is acceptable to submit these items for a representative product the ingredient information of which is described in the column for "Ingredients of product" in Attached Form 2 for quasi-drugs, etc. among products constituting the series. However, if PMDA requests the submission for other products in the series, these items shall be promptly submitted.
  - (c) It is acceptable to submit these items only at the time of the first report. However, if an additional report is subsequently submitted and descriptions related to the reported contents have been changed from those submitted in the previous report, the latest version should be submitted again. If the descriptions related to the reported contents have been changed, submit them with an additional report.
- If the primary suspected product is changed, submit a copy of description on immediate containers, etc. of the new primary suspected product and description in its package insert, etc. with an additional report.
- (d) If the documents to be submitted as a copy of the description on immediate

containers, etc. include the description in the package insert, etc., it is acceptable to submit only a copy of the description on immediate containers, etc.

#### 7. Reception ledger

When submitting reports in CD, etc. or paper-based media to the reception, the reporting company shall enter necessary information in the reception ledger at the reception according to the following classification and keep the reference number.

(Reception ledgers for post-marketing reports of adverse reactions, etc. [excluding reports of adverse reactions to quasi-drugs, etc.] )

a	Post-marketing reports of adverse reactions in Japan (first reports)
b	Post-marketing reports of adverse reactions in Japan (additional reports)
c	Post-marketing reports of overseas adverse reactions (first reports)
d	Post-marketing reports of overseas adverse reactions (additional reports)
e	Post-marketing reports of infections in Japan and overseas
f	Post-marketing research reports (drugs, quasi-drugs, and cosmetics)
g	Post-marketing foreign corrective action reports
h	Post-marketing withdrawal reports
i	Post-marketing re-submission

(Reception ledgers for reports of adverse reactions, etc. in clinical trials)

j	Reports of adverse reactions in Japan in clinical trials (first reports)
k	Reports of adverse reactions in Japan in clinical trials (additional reports)
l	Reports of overseas adverse reactions in clinical trials (first reports)
m	Reports of overseas adverse reactions in clinical trials (additional reports)
n	Reports of infections in Japan and overseas in clinical trials
o	Research reports in clinical trials
p	Foreign corrective action reports in clinical trials
q	Withdrawal reports in clinical trials
r	Re-submission in clinical trials

(Reception ledgers for reports of adverse reactions to quasi-drugs, etc.)

s	Reports of adverse reactions to quasi-drugs
t	Reports of adverse reactions to cosmetics

\*The reception ledgers, h and i, are used for withdrawal reports and re-submission, respectively, of reports of adverse reactions to quasi-drugs, etc.

#### 8. Registration of provisional codes, etc. related to post-marketing reports of adverse reactions, etc.

The drug codes to be used for post-marketing reports of adverse reactions, etc. require registration or application for issuance in advance. For registration or application for issuance

in (1) to (4), contact the Information Management Section, Office of Informatics and Management for Safety, PMDA by fax, etc.

(1) For prescription drugs

For the drugs related to reporting, enter the test substance identification code as a provisional code in the “Medicinal Product Name as Reported by the Primary Source (G.k.2.2)” and “Substance / Specified Substance Name (G.k.2.3.r.1)” during the period after approval until “Prescription drug data file (code table)” (re-examination code) is given. If the clinical trial notification has not been submitted for the test substance identification code concerned, register it as a provisional code using Appendix 9, “Provisional Code Registration Form.” If the clinical trial notification has been submitted, registration of the provisional code is not necessary. Enter the test substance identification code provided in the protocol in the report as a provisional code.

(2) For over-the-counter drugs and drugs requiring guidance

If a drug related to reporting is not listed in the “Drug brand codes,” register a “drug brand code” in advance with the Economic Affairs Division, Health Policy Bureau, Ministry of Health, Labour and Welfare, and register the registered code using Appendix 9.

(3) For in vitro diagnostics or pharmacy-made pharmaceuticals

PMDA issues codes for reporting adverse reactions, etc. for in vitro diagnostics or pharmacy-made pharmaceuticals. If no code related to reporting has been assigned to the in vitro diagnostics, apply for issuance of the code in advance, using Appendix 10 “Application Form for Codes for Reporting Adverse Reactions, etc. to In Vitro Diagnostics.” The issued code shall be communicated to the code applicant by fax, etc.

(4) For quasi-drugs and cosmetics

PMDA issues the product codes of quasi-drugs and cosmetics. If no product code related to reporting has been assigned, apply for issuance of the code using Appendix 11 “Application Form for Product Codes of Quasi-drugs and Cosmetics.” The issued code shall be communicated to the code applicant by fax, etc. Be careful not to apply for issuance of a code in duplicate for a product for which a code has already been issued.

9. Other

(1) Sender identifiers

A. In the case of new registration or change, submit Appendix 2, “Sender Identifier Application Form,” to the Information Management Section, Office of Informatics and Management for Safety, PMDA.

B. Even for reasons other than merger/succession, the sender identifier may be changed if deemed necessary.

C. If a change in sender identifier is desired, the reason for change shall be entered in the remarks column.

D. Only half-width alphanumeric characters and half-width underscore ( \_ ) can be used in sender identifiers, and the maximum number of characters is 60.

E. If multiple sender identifiers are required for reasons such as integration of systems for reporting adverse reactions, etc. at companies, these identifiers can be used simultaneously only for a certain period. However, when the system integration is completed, they should be integrated into one sender identifier. For details, contact the Information Management Section, Office of Informatics and Management for Safety, PMDA.

(2) Information on companies/persons in charge

The latest information on companies/persons in charge should always be registered with Information Management Section, Office of Informatics and Management for Safety, PMDA using Appendix 3, “Registration Form for Companies Reporting Adverse Reactions, etc. and Persons in Charge.” In particular, since ACK files and error notifications will be sent to the representative e-mail address, any change in the representative e-mail address should be promptly communicated.

The information on companies/persons in charge can also be registered on the reporting site, and in this case, it is not necessary to submit Appendix 3. If the reporting site is available, reporters’ cooperation by registering/changing the information on the reporting site is appreciated.

If no report will be made in the future because the company does not have a marketing business for drugs or quasi-drugs, etc. because of succession of drugs or quasi-drugs, etc. or merger, etc. of companies, describe the contents of registration in each item in Appendix 3, describe the reason for deletion of registration in the remarks column, and contact the Information Management Section, Office of Informatics and Management for Safety, PMDA.

(3) When applying for the use of the reporting site, use Appendix 8 and submit the application to the Information Management Section, Office of Informatics and Management for Safety, PMDA by fax, etc. Refer to the SKW site for contact information. When submitting the application by postal mail, etc., write in red “Application Form for Use of Reporting Site” on the front of the envelope to be sent.

### **Technical Matters Related to Preparation, etc. of ICSR File in Reporting of Adverse Reactions, etc.**

When reporting an adverse reaction, etc., it is necessary to prepare an ICSR file whether it is reported by electronic reporting, CD, etc., paper-based method, or e-mail. Prepare the ICSR file paying attention to the following technical matters.

#### 1. Electronic reporting

- (1) Three types of electronic reporting are possible.
  - A. Reporting in accordance with the AS1 specifications (SMTP) using the EDI tool (hereinafter referred to as the “AS1”)
  - B. Reporting in accordance with the AS2 specifications (HTTPS) using the EDI tool (hereinafter referred to as the “AS2”)
  - C. Reporting by uploading at the PMDA ICSR reporting site (website)

#### (2) Restrictions in electronic reporting

- A. Although it is possible to electronically report multiple cases as one batch, a single case must also be reported as one batch.
- B. A “Post-marketing report of adverse reactions, etc.” and a “Report of adverse reactions, etc. in clinical trials” cannot be included in one batch.
- C. The maximum number of cases per batch is 1000. The file size per batch is shown below.

Transmission method	Maximum file size per batch
Reporting with the AS1	10 MB
Reporting with the AS2	50 MB
Reporting via the reporting site	100 MB

#### (3) Points to consider in transmission

- A. Common points
  - (a) Confirm that there are no errors in the ICSR file.
  - (b) The file of submission data should be checked for virus in advance, encoded, and attached to the ICSR file.
- B. Reporting with the AS1 or AS2
  - (a) Sign and encrypt using the EDI tool.
  - (b) When reporting with the AS1, send the report to the e-mail address for reporting adverse reactions, etc. When reporting with the AS2, connect to the specified URL. The e-mail address or URL for reporting adverse reactions, etc. shall be communicated using Appendix 12 at the time of conducting the connection confirmation test.
  - (c) When reporting with the AS1 or AS2, check the MDN to confirm that the report has been received.
- C. Reporting via the reporting site
  - (a) Sign and encrypt using the R3 signature/encryption tool provided by PMDA.

(b) Connect to the reporting site and upload the ICSR file.

(4) Communication protocol, electronic certificate, etc.

A. Communication protocol

[1] AS1:SMTP

[2] AS2:HTTPS

Communication using AS2 requires a separate SSL server certificate.

[3] Reporting site: HTTPS

B. Electronic certificate

Electronic certificates meeting the following specifications shall be used.

- Format: X.509 Version 3
- Public key length in electronic certificate: RSA2048 bit
- Signature algorithm: SHA256
- A corporation should use the electronic certificate (electronic signature) of the representative.
- When reporting using the AS1 or AS2, be sure to perform the connection confirmation test using a new electronic certificate before the expiration date, and register the new public key using Appendix 6. In the case of reporting via the reporting site, be sure to register for the reporting site and the R3 signature/encryption tool before the expiration date. If the electronic certificate expires or electronic reporting is no longer made, contact the Information Management Section, Office of Informatics and Management for Safety, PMDA promptly.

C. Encryption/electronic signature

- Encryption function: S/MIME version 2 or higher
- Public key encryption method: RSA (PKCS#1 version 1.5)
- Common key encryption method: AES
- Hash function: SHA256

D. Other

An additional report should be made after the previous ACK message is received. Do not include the same case in a batch report.

E. Measures to be taken at the time of failure

The system may be suspended in the event of natural disaster, other emergency, serious system failure or any other unavoidable reason. When the system is suspended, electronic reports cannot be received and therefore, reports shall be submitted by paper-based reporting or reporting by CD, etc.

Such a situation will be promptly communicated to the registered representative e-mail addresses for post-marketing or clinical trial reporting and on the PMDA website.

2. Reporting by CD, etc. or paper-based reporting

For reporting by CD, etc. or paper-based reporting, the ICSR file containing reported matters shall be recorded on CD or DVD and submitted.

(1) Format of electronic media

A. CD-R (ROM)

Format: ISO 9660 standard level 3 and Joliet, Romeo

Size: 650 MB or 700 MB

B. DVD-R(ROM)

Format: ISO 9660 Universal Disk Format (UDF 2.00)

Size: 4.7 GB

(2) Points to consider in preparation

- A. Confirm that there are no errors in the ICSR file.
- B. Attached files should be encoded and attached to the ICSR file after virus check.
- C. Prepare the CD, etc. for each category of the reception ledger shown in 7. of Attachment 9. Multiple ICSR files or folders may be saved in one CD, etc.

3. Reporting by e-mail

For reporting by e-mail, the ICSR file containing the reported matters shall be submitted by attaching it to the e-mail.

(1) E-mail address to which reports should be sent

To be communicated separately.

(2) Points to consider in transmission

- A. The “Subject (title)” of the e-mail shall be “Sender identifier”-“Unique case number”-“Report date.”

Example) senderid-0001-20170401

- B. It is not necessary to include text in the e-mail, but if it is re-submission, describe this.
- C. One ICSR file shall be attached to one e-mail, and ICSR files of multiple reports shall not be attached. If a file of accompanying documents is also attached, only the file of accompanying documents for the report concerned can be attached.
- D. If it is not possible to send an e-mail with the ICSR file and all files of accompanying documents for the report concerned because of the restriction of the e-mail size, divide these files for sending them multiple times. However, the “subject (title)” of all e-mails should be the same and as shown in A. above.

In the body of the first e-mail to be sent, state that the files will be sent by dividing them multiple times.

The maximum e-mail size that can be sent at one time is 10 MB.

- E. Confirm that there are no errors in the ICSR file.
- F. The file of submission data should be checked for virus in advance, encoded, and attached to the ICSR file.

4. Preparation of ICSR files

- A. The ICSR file preparation tool and the ICSR file preparation tool for quasi-drugs, etc. are posted on the SKW site. If necessary, download the tool to create ICSR files. The tools are updated appropriately. When using a tool, check whether it is the latest version each time before using.
- B. By using the ICSR file preparation tool and the ICSR file preparation tool for quasi-drugs, etc., ICSR files for all reporting categories indicated in the attachment of the 2020 E2B (R3) Two Director Notification can be prepared.
- C. The ICSR files prepared using the ICSR file preparation tool and the ICSR file preparation tool for quasi-drugs, etc. can be used for electronic reporting, reporting by CD, etc., paper-based reporting, or reporting by e-mail.

## 5. Naming conventions and file formats for ICSR files

ICSR files shall be named according to the following rules. Or, make sure that each file name is unique. Only half-width alphanumeric characters and half-width hyphens (-) can be used in file names (except for the half-width underscore [\_] included in sender identifiers).

### A. ICSR file (for reporting with the AS1 or AS2, reporting by CD, etc., or paper-based reporting)

File name: I-Sender identifier-Report date-Unique case number.xml (half-width alphanumeric characters)

Example) I-senderid-20170401-1.xml

File format: XML

### B. ICSR file (for reporting via the reporting site)

File name: I-Sender identifier-Report date-Unique case number.enc (half-width alphanumeric characters)

Example) I-senderid-20170401-1.enc

File format: enc (encrypted/signed/ZIP compressed with the R3 signature/encryption tool provided by PMDA)

### C. ACK file (for reporting with the AS1 or AS2, reporting by CD, etc., or paper-based reporting)

File name: A-Sender identifier-Report date-Unique case number.xml (half-width alphanumeric characters)

Example) A-senderid-20170401-1.xml

File format: XML

### D. ACK transmission file (for reporting via the reporting site)

File name: A-Sender identifier-Report date-Unique case number.enc (half-width alphanumeric characters)

Example) A-senderid-20170401-1.enc

File format: enc (encrypted/signed/ZIP compressed; decryption/signature confirmation/unzipping can be done with the R3 signature/encryption tool provided by PMDA)

6. ACK files and error notifications, etc.

An ACK file will be sent whether the report is made by electronic reporting, reporting by CD, etc., or paper-based reporting. Be sure to confirm the contents.

Before sending an additional report, be sure to wait for the ACK file of the previous report and confirm that it has been received. Note that in electronic reporting, if an additional report is sent before the ACK file is sent by PMDA in reply, it is considered as an error and the additional report will not be accepted.

(1) ACK file destination

In electronic reporting, the ACK file is sent after signing and encrypting. In reporting via the reporting site, decrypt using the R3 signature/encryption tool to confirm the contents. Destination of ACK files is as follows.

Electronic reporting	Reporting with the AS1	E-mail address dedicated for transmission/reception
	Reporting with the AS2	Linked electronic data processing system
	Reporting via the reporting site	Registered representative e-mail address for post-marketing or clinical trial reporting
Reporting by CD, etc.		Registered representative e-mail address for post-marketing or clinical trial reporting
Paper-based reporting		Registered representative e-mail address for post-marketing or clinical trial reporting
Reporting by e-mail		Registered representative e-mail address for post-marketing reporting

- A. If ICSR files submitted in reporting by CD, etc., paper-based reporting, or reporting by e-mail cannot be loaded into the system because of XML parse errors, improper attachment of files, errors in file names, etc., notify of this using the registered representative e-mail address for post-marketing or clinical trial reporting.
- B. Re-submission of CD, etc. shall be notified to the registered person in charge of post-marketing or clinical trial reporting of adverse reactions, etc. Actions shall be taken in response to the notification.
- C. If the representative e-mail address of post-marketing or clinical trial reporting has not been registered, the contents, etc. in A above shall be notified to the person in charge of reporting of adverse reactions, etc. Actions shall be taken in response to the notification.
- D. If the ACK file cannot be confirmed and no error notification has been received at the representative e-mail address, contact the Information Management Section, Office of Informatics and Management for Safety, PMDA.
- E. In reporting by CD, etc., paper-based reporting, or reporting by e-mail, PMDA shall, in principle, send the ACK file to the representative e-mail address by the day after the day of the report, etc. received (excluding Saturdays, Sundays, and holidays). If it is confirmed that PMDA could not reply to the representative e-mail address, PMDA will contact the registered person in charge of reporting of adverse reactions, etc. by phone or fax, etc. Be careful to register the representative e-mail address, the person in charge of reporting of adverse reactions, etc., phone number, and fax number without omission. If the report has been submitted to the reception or sent by postal mail, etc. and PMDA has not contacted within 3 days including the day of receipt (excluding Saturdays,

Sundays, and holidays), contact the Information Management Section, Office of Informatics and Management for Safety, PMDA for post-marketing reporting, or the Review Planning Division, Office of Review Management, PMDA for clinical trial reporting.

(2) Contents of ACK file and response

- A. If “AR” is selected for “ACK.A.4. Transmission Acknowledgement Code” among ACK message data elements, the reports have not been received on any of the cases in the batch concerned, and therefore the contents should be corrected and re-submitted.
- B. If “CR” is selected for “ACK.B.r.6 Acknowledgement Code for an ICSR Message,” it indicates that the report concerned cannot be received, and therefore the report should be corrected and sent again. Even if “CA” is selected for “ACK.B.r.6 Acknowledgement Code for a ICSR Message,” if there is an error code in “ACK.B.r.7 Error / Warning Message or Comment,” the report has been received but there is an error. Therefore, the contents should be corrected, and an additional report should be made.
- C. Error codes are listed in “ACK.B.r.7 Error / Warning Message or Comment.” When there are multiple errors, up to 20 errors shall be entered by separating them by comma (“,”). If there are more than 20 errors, the number of errors that were not included in “ACK.B.r.7 Error / Warning Message or Comment” shall be entered in 3 digits at the end. If the number cannot be expressed in 3 digits, “999” shall be entered.
- D. Error codes that are not listed in the ACK file can be found on the reporting site.
- E. The received reports are described in the format, “Reporting category-Identification number-Number of PMDA reports” in “ACK.B.r.2 Local Report Number,” so confirm it.
- F. A report shall be received as a completion report if it is received with “J2.7.1 Complete / Incomplete Category” among J data elements populated with “completed” and, among ACK message data elements, “ACK.A.4. Transmission Acknowledgement Code” populated with “AA” or “AE” and “ACK.B.r.6 Acknowledgement Code for a ICSR Message” for the report concerned populated with “CA,” without any error code in “ACK.B.r.7 Error / Warning Message or Comment.” Otherwise, be sure to make an additional report or re-send the report.
- G. The report shall be received as a withdrawal report if, among the ACK message data elements, “ACK.A.4. Transmission Acknowledgement Code” is “AA” or “AE,” the “ACK.B.r.6 Acknowledgement Code for a ICSR Message” for the report concerned is “CA,” and there is no error code in “ACK.B.r.7 Error / Warning Message or Comment.” Otherwise, the report shall be re-sent.

(3) File formats, etc. that cannot be received

- A. Parse error files
- B. Files with invalid file names (files violating the file name rules shown in 4 of Attachment 7 for the file names of submission data, or 5 of Attachment 10 for ICSR file names)
- C. Files with invalid formats (formats shown in 1. (5) of Attachment 7 for submission data, or formats other than xml or enc for ICSR files)

D. Files infected with virus (files found to be infected with virus in virus check of the system)

## Glossary

- **Pharmaceuticals and Medical Devices Act**  
Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960)
- **Regulation**  
Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ministry of Health and Welfare Ordinance No. 1 of 1961)
- **Post-marketing Director-General Notification**  
PFBSB Notification No. 1002-20 of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 2, 2014, “Reporting of Adverse Reactions, etc. to Drugs, etc.” (partially revised on March 31, 2016)
- **Clinical Trial Director-General Notification**  
PSEHB Notification No. 0831-8 of the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020, “Reports of Adverse Reactions, etc. in Clinical Trials to Pharmaceuticals and Medical Devices Agency”
- **Quasi-drugs, etc. Director-General Notification**  
PSEHB Notification No. 0331-7 of the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 31, 2017, “Reporting of Adverse Reactions, etc. to Quasi-drugs and Cosmetics”
- **E2B (R3) Implementation Guide Notification**  
PFBSB/ELD Notification No. 0708-5, PFBSB/SD Notification No. 0708-1 issued jointly by the Director of Evaluation and Licensing Division and the Director of Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated July 8, 2013, “Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs)” (partially revised on March 15, 2017)
- **2017 E2B (R3) Two Director Notification**  
PSEHB/PED Notification No. 0331-6, PSEHB/SD Notification No. 0331-1 issued jointly by the Director of Pharmaceutical Evaluation Division and the Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 31, 2017, “Post-marketing Reports of Adverse Reactions, etc. and Reports of Adverse Reactions, etc. in Clinical Trials According To E2B (R3) Implementation Guide”
- **2020 E2B (R3) Two Director Notification**  
PSEHB/PED Notification No. 0831-12, PSEHB/PSD Notification No. 0831-3 issued jointly by the Director of Pharmaceutical Evaluation Division and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020, “Post-marketing

Reports of Adverse Reactions, etc. and Reports of Adverse Reactions, etc. in Clinical Trials According To the E2B (R3) Implementation Guide”

- Post-marketing reports of adverse reactions, etc.  
Reporting of adverse reactions, etc. specified in Article 68-10, Paragraph 1 of the Pharmaceuticals and Medical Devices Act.  
The term refers to the reporting categories of AA, AB, AC, AD, AE, AF, AG, BA, BB, BC, and BD among those listed in Attachment 1 of the 2020 E2B (R3) Two Director Notification.
- Reports of adverse reactions, etc. in clinical trials  
Reporting of adverse reactions, etc. related to clinical trials specified in Article 80-2, Paragraph 6 of the Pharmaceuticals and Medical Devices Act.  
The term refers to the reporting categories of DA, DB, DC, DD, DE, DF, and DG among those listed in Attachment 1 of the 2020 E2B (R3) Two Director Notification.
- Test drug  
A drug that is investigated in a clinical trial, and the application for marketing approval of the drug concerned based on the results of the clinical trial is intended.
- Main test drug  
The term refers to a drug specified as the main test drug in the clinical trial notification.
- Study drug  
The term refers to a test drug, comparator, coadministered drug, rescue drug, premedication drug, etc. specified in the protocol to be used for evaluation of the efficacy and safety of the test drug. A study drug can be used regardless of whether its active ingredient has been approved in Japan or overseas.
- Attached forms  
Attached Forms 1 to 6 of the Post-marketing Director-General Notification and Attached Forms 1 to 6 of the Clinical Trial Director-General Notification
- Attached forms for quasi-drugs, etc.  
Attached Forms 1 and 2 of the Quasi-drugs, etc. Director-General Notification
- J data elements  
Elements listed in Appendix 1, “Data elements for system management of the Ministry of Health, Labour and Welfare,” of the 2020 E2B (R3) Two Director Notification
- E2B data elements  
Elements listed in Chapter 3.4 of Attachment 1, “Implementation guide for electronic transmission of Individual Case Safety Reports (ICSRs),” of the E2B (R3) Implementation Guide Notification.
- Elements for acknowledgement message (ACK message)  
Elements listed in Chapter 4.2 of Attachment 1, “Implementation guide for electronic transmission of Individual Case Safety Reports (ICSRs),” of the E2B (R3) Implementation Guide Notification and Appendix 6, “Elements for acknowledgement

messages for Individual Case Safety Reports (ICSRs),” of the 2020 E2B (R3) Two Director Notification.

- Electronic reporting  
Reporting by submitting the ICSR files via the EDI tool or the reporting site.
- Reporting by CD, etc.  
Reporting by recording the ICSR files on CD, etc. and simultaneously submitting documents describing necessary items specified in the 2020 E2B (R3) Two Director Notification with CD, etc. However, it cannot be used for reports of adverse reactions to quasi-drugs, etc.  
CD, etc. refers to CD-R (ROM) or DVD-R (ROM).
- Paper-based reporting  
Reporting by submitting the report describing the necessary items specified in the attached forms of the Post-marketing Director-General Notification, the attached forms of the Clinical Trial Director-General Notification, or the attached forms for quasi-drugs, etc., and records of the ICSR file in CD, etc.  
CD, etc. refers to CD-R (ROM) or DVD-R (ROM).
- Reporting by e-mail  
Reporting by e-mail can be applied only to the reporting of adverse reactions to quasi-drugs, etc. Reporting by submitting the report containing the necessary items specified in the attached forms for quasi-drugs, etc., and the ICSR file as an attachment to an e-mail.
- Immediate reports  
Reports corresponding to 2 (1) [2] of the attachment of the Post-marketing Director-General Notification.
- Immediate reports (reports of adverse reactions, etc. in clinical trials)  
The term refers to reporting in an emergency situation that requires discontinuation of the clinical trial, which is implemented by describing the applicable items in the attached forms of the Clinical Trial Director-General Notification and submitting by e-mail, etc. or other electronic methods.
- Withdrawal reports  
The term refers to the reports for the purpose of withdrawing reports in the cases including reporting of wrong “C.1.1 Sender’s (case) Safety Report Unique Identifier,” etc.
- ICSR file  
A file in XML format prepared in accordance with the specifications shown in the E2B (R3) Implementation Guide Notification, entering the elements listed in Attached Form 1, “Data elements for system management of the Ministry of Health, Labour and Welfare,” and Attached Form 2, “Data elements for acknowledgement message in Individual Case Safety Reports,” of the 2020 E2B (R3) Two Director Notification.
- ACK file  
A file containing the elements for the acknowledgement message prepared in XML format.

- **Batch report file**  
A unit for reporting individual case reports, etc. One batch report file includes the report of at least one case.
- **Submission data**  
Submission data including relevant literature, CCDS, images (X-ray, ECG, etc.), etc. to be attached to individual case safety reports.
- **Archive**  
To put together multiple files.
- **This system**  
The electronic data processing system owned by PMDA that receives and processes reports of adverse reactions, etc.
- **Reporting site**  
PMDA ICSR reporting site.  
ICSR files can be submitted, their receipt status can be checked, and the contents of ACK files can be checked.
- **ICSR file creation tool/ICSR file creation tool for quasi-drugs, etc.**  
Using this tool, ICSR files for each reporting category can be prepared, errors can be checked, and the files can be output as attached forms for the reporting categories of AA to AG and DA to DG.  
Similarly, the ICSR file creation tool for quasi-drugs, etc. will be separately provided for the reporting categories of BA to BD.
- **R3 signature/encryption tool**  
A tool provided by PMDA for electronic signature and encryption of ICSR files. If submitting reports via the reporting site, the reports need to be signed and encrypted using this tool.
- **EDI tool**  
A software for electronic exchange of reports of adverse reactions, etc.
- **MDN (Message Disposition Notifications)**  
E-mail message opening notification function which is automatically carried out by the EDI tool (the function to reject the denial of receipt)
- **Error notification**  
An error message to notify that an ACK file cannot be sent in reply.

- E-mail address for reporting adverse reactions, etc.  
PMDA e-mail address dedicated for reporting of adverse reactions, etc. (the same e-mail address for post-marketing and clinical trial reporting).
- E-mail address dedicated for transmission/reception  
The e-mail address of each reporting company dedicated for reporting of adverse reactions, etc. (the same e-mail address for post-marketing and clinical trial reporting).  
Used to send ACK files for reporting with AS1.
- Representative e-mail address  
Contact e-mail address.  
Used for error notifications in electronic reporting.  
For reporting via the reporting site, paper-based reporting, and reporting by CD, etc., this e-mail address is used to send ACK files and error notifications.  
It is also used as contact in case of failures of this system, etc.