Guidance for Industry

E2B(M): Data Elements for Transmission of Individual Case Safety Reports

Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2004
ICH

Revision 1

Guidance for Industry

E2B(M): Data Elements for Transmission of Individual Case Safety Reports

---

Questions and Answers

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2004
ICH

Revision 1

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1]
E2B(M): Data Elements for Transmission of Individual Case Safety Reports

Questions and Answers

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if that approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This question and answer (Q&A) guidance is intended to assist applicants who plan the electronic transmission of individual case safety reports (ICSRs) to the Food and Drug Administration (FDA). The guidance is a revision of the E2B(M) Q&A guidance that was published in October 2003. The guidance provides answers to questions that have arisen since the finalization of the ICH E2B(M) guidance, version 4.4.1, and the M2 specification document, version 2.3. This Q&A quidance is not meant to be all inclusive, as further questions may be addressed in the future.[2] The questions and answers provided here reflect the consensus of the ICH parties.

[1] This guidance was developed within the E2B(M) Implementation Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 11, 2003. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Further questions or comments related to the E2B(M) guidance can be submitted to: question-to-E2BM-guideline@ich.org. Version 3.0 of the E2B(M) Implementation Working Group Questions and Answers, dated November 11, 2003, can also be viewed on the ICH Web site under Publications/Guidelines/Efficacy Guidelines/Clinical Safety.

Questions concerning the time frame or specific U.S. requirements that are not answered by the E2B(M) guidance should be addressed directly to the FDA.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The ICH guidance *E2B Data Elements for Transmission of Individual Case Safety Reports* was signed off by the International Conference on Harmonisation (ICH) in July 1997 and issued by the FDA in January 1998. ICH subsequently issued a revised guidance, E2B(M), to provide additional information and clarification. The revised guidance incorporated adjustments based on the successful pilot projects being conducted in the three ICH regions. ICH signed off on E2B(M) in November 2001, and the FDA issued the revised guidance in April 2002.

III. QUESTIONS AND ANSWERS

Q1: During the period of transition, as health authorities or pharmaceutical companies migrate from paper to electronic ICSR submissions and exchanges using E2B(M)/M2 standards, certain ICSRs will likely be exchanged in both paper and electronic format. This could occur either because the initial ICSR was on paper and the follow-up is in electronic format or because the two parties are in a pilot program where they are exchanging ICSRs in both paper and electronic format. Two questions arise:

Question 1a: How can two or more exchanges of the same ICSR be linked together to avoid a duplicate report?

Question 1b: How can the current paper forms accommodate the full ICH format of the worldwide unique case identifier?

A1: Answer 1a: Compliant with the definition of field A.1.0.1, the ICH format of the worldwide unique case identifier (country code-company or regulator name-report number) should always be used, and copied into field A.1.10.1 or A.1.10.2. as appropriate.

In the event that the ICSR either has been exchanged by the two parties in the past using a different identifier or that it is exchanged simultaneously with a different identifier, this other identifier should be listed in field A.1.11.2 and the organization’s name should be

---

Questions requiring immediate answers should be addressed directly to the FDA. It is anticipated that subsequent ICH Q&A documents will be developed and approved by the ICH Steering Committee approximately every 6 months.

captured in field A.1.11.1, consistent with the definition of the A.1.11 field for the identification of duplicates.

This recommendation applies to DTD version 2.0 and DTD version 2.1.

Answer 1b: In case the ICH conforming worldwide unique case identifier cannot be accommodated on the paper forms, it is recommended that the report number alone (without the country code or the company or regulator name) be used.

Q2: For fields where only one MedDRA coding level is accommodated, should I use PT or LLT?

Section B.2 contains fields B.2.i.0, B.2.i.1 and B.2.i.2 to capture the verbatim term, LLT and PT, respectively. However, sections B.1.7.1a, B.1.8f, B.1.8g, B.1.9.2, B.1.9.4, B.1.10.7.1a, B.1.10.8f, B.1.10.8g, B.4.k.11, B.4.k.17.2, B.4.k.18.1, B.5.3 contain only one field and do not specify whether the LLT or PT should be used.

A2: For the ICH E2B(M) fields B.1.7.1a, B.1.8f, B.1.8g, B.1.9.2, B.1.9.4, B.1.10.7.1a, B.1.10.8f, B.1.10.8g, B.4.k.11, B.4.k.17.2, B.4.k.18.1, B.5.3 the following should be used:

- For EU regulators: LLTs
- For FDA: PTs
- For MHLW: PTs

Q3: What is the process to maintain, add, modify, or delete entries in the code lists in attachments 1 and 2 of E2B(M)?

A3: Currently these lists cannot be modified.

Q4: The current definition of B.4.k.7 calls for the use of free text until a controlled vocabulary is available. Is a harmonized vocabulary for pharmaceutical dosage forms available?

A4: There is currently no harmonized vocabulary for pharmaceutical dosage forms. Until an ICH vocabulary is available, the following should be used:

- For EU Regulators: the European Pharmacopoeia standard list
- For FDA: Free text
- For MHLW: The list of pharmaceutical forms as made available by MHLW

Q5: How can I send product-specific registration or other regulatory administrative information to multiple receivers in a single transmission?

A5: A single transmission for administrative information of an ICSR to multiple receivers in the ICH regions is currently not possible.

Various health authorities have engaged in production or pilot programs to implement E2B(M). A need to capture in more detail registration–related information (similar to the existing paper submission process using fax cover sheets or regulatory forms) became evident. As a consequence, local guidance has been introduced to transmit additional information accompanying each ICSR:

- For EU Regulators: see E2B section B.4.k.4.
- For FDA: Field B.4.k.4.1. should contain the NDA, BLA or STN number in the appropriate format.
- For MHLW: Each ICSR should be accompanied by a corresponding J-file, as detailed in the relevant MHLW guidance documents.

Q6: What language should I use for an ICSR transmission?

A6: For EU Regulators: ICSRs in English are generally accepted. However, there can be local requirements for a translation of the case narrative in the official local language.

For FDA: English

For MHLW: Japanese

Q7: How can I submit a causality or scientific assessment in either an algorithmic or text representation in the current E2B(M) format?

A7: The current structure of E2B(M) includes fields B.4.k.18.1-4, which allow the sender to indicate such assessments for each drug-event combination.

In addition, field B.5.4 can be used to further elaborate the sender's position or assessment. Local regulatory requirements regarding expedited and periodic reporting determine whether inclusion of sponsor assessments is necessary.

Q8: How can I identify the primary source and the reporter qualification when an ICSR is forwarded by health authorities with minimal or no information on the primary source?

A8: If no information on the primary source is available, section A.2.1 should identify the health authority as the primary source. Field A.2.1.4 'Qualification' should be populated with a code of "3" (Other health professional).

In addition, field A.1.4 'Type of report' should be populated with a code of "4" (Not available to sender (unknown), if appropriate.

Q9: How can I identify the study name, the study number, the patient, and the drug in clinical trials to be reported to the EU regulators and MHLW in the E2B(M) format?

A9: The code list of 'Study type' in field A.2.3.3. is very short, so the type of study should be characterized more clearly in the study name. For a more explicit description of the study beyond 100 characters, the full study name should be given in the case narrative. In addition, some regulatory authorities request the additional submission of a regulatory study number (e.g., EUDRACT number). For this situation, the study name in element A.2.3.1 should be a concatenation of the EUDRACT number and the 'Study name,' i.e., EUDRACT number-Study name.

The 'Study number' in field A.2.3.2 should be the sponsor study number.

The patient identification in a clinical trial can be transmitted in field B.1.1.1d 'Patient investigation number.' Note that multiple elements from the source database, like Center-Patient and random number, should be concatenated in this element to ensure a unique patient identification.

The trial drug identification is possible through the usual elements for the description of the suspected drug B.4.k.2.1 and B.4.k.2.2. For some countries, the project-related regulatory drug identification number can be submitted in field B.4.k.4.

The present version of E2B(M) allows for the distinction of unblinded vs. blinded information.

Q10: There may be cases where for one drug, one or more formulation/dosage, lot number and indication are provided. How should this information be presented in the electronic transmission?

A10: The drug section B.4 is a repeatable block.

If for one drug there is information on multiple dosages/formulations or indications, the entire section should be repeated to capture all the information.

For lot numbers, the guidance allows for multiple batch/lot numbers in the same field B.4.k.3. However, it is recommended that the drug section B.4 be repeated.

Q11: Field B.1.2.1 'Patient birth date' provides for population with a full date format including day, month, year. If incomplete dates are reported, how should these be presented?

A11: If an incomplete date of birth is reported, then the field B.1.2.2. 'Age at the time of onset of reaction/event' should be used, as indicated in the user guidance. Alternatively, field B.1.2.3 'Patient age group (as per reporter)' can be used to indicate the age of the patient.

Q12: Do the concepts of parent child reporting as described in the ICH E2B(M) guideline also apply to a fetus or an unborn child?

A12: All reports affecting a fetus or an unborn child should be recorded as parent-child reports with the appropriate sections of E2B(M) completed.

Q13: Where in the E2B(M) message should a patient's drug allergy history be reported e.g., reporter has stated that the patient has an allergy to aspirin? There is no indication in the report as to whether the patient previously took the medication as treatment and had an allergic reaction or whether this knowledge came from patch testing.

In addition, reports of drug allergy history are often subjective and can be erroneous. MedDRA terms are available for allergies to insulin and a few antibiotics (sulfonamide, penicillin) but few drugs are specifically named in conjunction with the allergy.

A13: It might be advisable to obtain additional information from the primary reporter.
If it is the first allergic reaction for the patient and allergy testing results are available, they can be recorded along with other ADR-related terms. For example, the reaction itself is coded to the PT "Drug hypersensitivity" (or a more descriptive LLT) in B.2.i.1 or B.2.i.2. In addition, the testing results are recorded by use of the PT "Skin test positive", or "Allergy test positive" (or their more descriptive LLTs) in B.2.i.1 or B.2.i.2.

Relevant past drug history, such as a history of allergy to a particular drug, can be reported in repeatable section B.1.8, using the suspect drug name and MedDRA terms in the indication and reactions fields.

The information could also be reported in section B.1.7.1, "Structured information on relevant medical history..." by using the PT "Drug hypersensitivity" (or a more descriptive LLT) under "Disease / surgical procedure / etc." , and the name of the drug under "comments". This latter field is not searchable in most databases and thus this is not the preferred option.

Q14: What is the time frame for a drug to be included in the drug history section or as a concomitant drug?

A14: This is a medical judgment that should be made by the medically-trained reporter and evaluator (e.g., in the company or health authority).

The decision should be based on the elimination half-life of the drug and the known pharmacodynamic effects of the drug in that particular patient (for example, a patient with known renal or liver impairment).

If it is unlikely that the product is still in the body and if there are no biologic effects known or suspected in that patient, the product should be listed in the medical history.

If the drug is still in the body or if there is a suggestion of biologic activity (even if the kinetics suggest complete elimination already) and if the reporter or the evaluator feel there is a possibility that the product played a role in the AE, then the product should be listed as a suspect drug. If the reporter and evaluator both agree that it is not a suspect drug, it should be listed as a co-medication (concomitant medication).

It is difficult to give an absolute time interval between the ingestion or use of the drug and the appearance of the AE. This is a medical judgment.

Overall, a conservative approach should be taken, and if there is any doubt, the product should be considered a suspect drug. If there are critical or controversial issues to be discussed in regard to this judgment, they can be briefly mentioned in the narrative.

As a general principal, all drugs that were completed/discontinued before the start of the treatment with the suspect(ed) drug(s) should be included in the 'Relevant drug history' section (B.1.8). Any drug(s) that are not suspected of causing the event or reaction and that are administered to the patient at the time the case is reported should be listed as concomitant medication.

Q15: Based on current experience it has become evident that the information collected for many of the E2B(M) fields is exceeding the current field lengths (e.g., A.1.8.2 'List of documents held by the sender,' A.2.3.1 'Study name,' B.4.k.6 'Dosage text,' B.2.i.0 'Reaction/event as reported by primary source,' B.5.1 'Case narrative,' B.5.2 'Reporter comment).

As the information can be critical to the report, there is the possibility that the sender organization could get into legal problems.

A15: As a general principle, it is recommended that the sender structure all available information on the case to the highest possible extent in the currently available E2B(M) fields.

The E2B(M) standards should be adhered to. Each sender is responsible for managing the information in the appropriate way.

Q16: ***We have an issue on reporting pregnancy cases which we would be very happy to get your opinion on:***

We have a study on pregnant women concerning diabetic patients. Up to 60% of these deliver by caesarean section (CS) either planned or emergency.

We suggest submitting linked serious adverse events reports as follows:

Scenario 1: Fetal distress and CS: One case on fetus (fetal distress), but none on the mother (CS). Follow-up on fetus: Event can be recoded to e.g., brain hypoxia: Outcome of event on fetus: e.g., recovered or recovered with sequelae of brain damage. If the mother suffers a complication, e.g., an infection in the wound, this could be another adverse event.

Scenario 2: Mother suffers from pre-eclampsia and the child is fine. One AE of pre-eclampsia on the mother. No event on the child.

Scenario 3: Mother suffers from pre-eclampsia and the child is small and a complication on the child occurs. One AE of pre-eclampsia on the mother. Just one code of Pre-eclampsia? or two codes one of pre-eclampsia and one of CS, one or more events on the child?

A16: The User Guidance, section B.1 (patient characteristics) states that in cases where a fetus or nursing infant sustains an adverse reaction/event, information on both the parent and child/fetus should be provided (referred to as parent-child/fetus report). If there has been no reaction/event affecting the child/fetus, the parent-child fetus report does not apply. For those cases describing fetal demise or early spontaneous abortion, only a parent report is applicable. If both the parent and the child/fetus sustain adverse events, two reports should be provided, but they should be linked using sections A.1.12 in each report. When only the child/fetus has an adverse reaction/event (other than early spontaneous abortion/fetal demise), the information provided in this section applies to the child/fetus and the characteristics concerning the parent who was the source of exposure should be provided in section B.1.10.

Scenario 1: As the author of the question suggests, only one SAE report should be completed for the mother, with the AE of fetal distress (recoded later to brain hypoxia). The caesarean section should not be considered an AE for the mother. The mother's characteristics should be captured in B.1.10.1 with the caesarean section as relevant medical history (B.1.10.7).

Scenario 2: As the author of the question suggests, only one SAE report should be completed for the mother, with the AE of pre-eclampsia. No events are reported for the child; therefore, a linked SAE report is not called for.

Scenario 3: Two linked SAE reports should be submitted: The mother's report should have the AE pre-eclampsia; the report for the fetus should have a term for fetal complication. The term pre-eclampsia would only apply to the mother's case. Section A.1.12 (ID number of the linked report) should be completed for both the mother and child's case.

Q 17: Can you provide more detailed user guidance on the use of 'Term highlighted by the reporter' (B.2.i.3)?

A17: All adverse reactions/events that occur at any point after introduction of the suspect drug/vaccine should be reported in E2B(M) section B.2 . Field B.2.i.0 should be used to report all reactions/events. Each reaction/event reported in the field B.2.i.0 should be coded in the fields B.2.i.1 (MedDRA LLT) or B.2.i.2 (MedDRA PT) or both, depending on regional preference. Field B.2.i.3 "Term highlighted by the reporter" is an optional field that, if used, should be correlated with medical concept(s) listed in field B.2.i.0. B.2.i.3 should be used to categorize the reactions/events as to (a) whether the medical concept was the reason the reporter contacted the company and (b) whether the medical concept is serious according to the company. If field B.2.i.3 is used, a single entry is selected from four listed numeric responses (1-4). The optional entries in B.2.i.3 should always map to entries in B.2.i.0.

This field is intended for the identification of a specific diagnosis as identified by the reporter, e.g., if the reporter specifies flu-like syndrome comprising of fever, chills, sneezing, myalgia and headache, then flu-like syndrome is the highlighted term.

If only one event is cited in a case report, this one is by implication considered highlighted by the reporter.

This field is optional for completion in the European Union and the United States but is mandatory in Japan for all complete case report types. For details, please consult MHLW guidance.

Q18: When is it intended to introduce a repeatable indication section within the drug section?

A18: DTD version 2.1 cannot currently be modified. Therefore, it is not possible to introduce a repeatable 'indication' section within the 'Drug(s) information' section B.4.

If for one drug there is information on multiple indications, the entire section B.4 should be repeated to capture all the specified indications (please refer also to user guidance as provided in E2BMIWG0011).

Q19: When is it intended to add the time zone information in M1.7 'Message date'?

A19: The fields M.1.7a 'Message date format' and M.1.7b 'Message date' allow the specification of the exact message date, including year, month, day, hour, minute, and second.

Information on the time zone cannot currently be accommodated in DTD version 2.0 or 2.1 since the specifications cannot be modified.

In general, the time specified in M.1.7 should always reflect the sender's time and time zone.

Q20: Practical experience has shown that it is important to capture seriousness criteria at reaction/event level.

How can this be handled within the current E2B(M) guideline?

A20: All seriousness criteria as specified in field A.1.5.2 'Seriousness criteria' apply to the case as a whole.

Field B.2.i.3 'Term highlighted by the reporter' can be used to identify the seriousness of each reaction/event that the primary source indicated was a major concern or reason for reporting the case.

Q21: For some time I have been looking, unfortunately without success, for an official message definition for a message to exchange company profiles including certificates between the organisations.

Is an official standardized message for this purpose available and if so where can I get the guideline / DTD / schema from?

A21: There is no ICH standard procedure for exchanging certificates (or public keys) of encryption software. However, in general, the use of safe and reliable procedures is recommended.
The procedures for exchanging certificates and public keys between health authorities and industry are specified in the regional legislation or guidelines.

EU: http://eudravigilance.emea.eu.int

Japan: http://www.pharmasys.gr.jp/e2bm2/e2bm2_index.html (Notification No.0630004/No.0630006 dated on 30 June 2003).

US: http://www.fda.gov/cder/aerssub

Q22: ICHE2B(M) refers to the basic elements for developing an electronic Serious Adverse Reaction Form.

In section B.2, Reaction(s)/Event(s) Description, it seems that more than one reaction could be described.

Does this mean that a syndrome should be divided into the different symptomatologies defining this syndrome (e.g., should flu syndrome be divided into headache, joint aches, etc.)? In that case, and as far as I understood, there is a concept discrepancy because requirements also says that a different form should be used for each serious adverse event.

A22: The purpose of the E2B(M) document is to standardize the data elements for the transmission of ICSRs. For advice on describing syndromes, please refer to the latest edition of the ICH document "MedDRA Term Selection: Points to Consider" as published at http://www.ich.org. At the time of this writing, advice is provided in sections on "Diagnosis reported with signs and symptoms" and "Provisional diagnoses."

B.2.i.1 and B.2.i.2 are repeatable fields, and a separate block should be used for each reaction/event term for the purpose of accommodating multiple reactions within a single report. A separate form should not be used for each serious adverse event occurring in the same patient with the same suspect product.