ICH **INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE**

E2B Implementation Working Group
Questions & Answers (R5)

Current version
dated March 3, 2005

In order to facilitate the implementation of the E2B guideline, the ICH Experts have developed a series of Q&As:

E2B Q&As
Document History

Version Number (First Codification)	Date	Description	New Codification November 2005
0.2	18 July 2003	Approval by the ICH Steering Committee	E2B Q&As
0.3	11 November 2003	Approval by the ICH Steering Committee of the newly added questions	E2B Q&As (R1)
0.4	10 June 2004	Approval by the ICH Steering Committee of the newly added questions	E2B Q&As (R2)
0.5	18 November 2004	Approval by the ICH Steering Committee of the newly added questions	E2B Q&As (R3)
1.0	7 January 2005	Deletion of the description for receiving questions on the introduction page. Revision of answer to question 30(a) (E2BM IWG 0050) in Q&A document.	E2B Q&As (R4)
1.1	3 March 2005	Correction of a mistyping : Response (a) of question **# 30** (*E2BM IWG0050*) : 3rd line from the bottom of that paragraph : "… populating the corresponding duration (B.4.k.15.a) fields (B.4.k.15a) and <803> (week) populating the two unit fields (B.4.k.15b)."	E2B Q&As (R5)

In November 2005, the ICH Steering Committee adopted a new codification system for ICH Guidelines. The purpose of this new codification is to ensure that the numbering / coding of ICH Guidelines is more logical, consistent and clearer. Because the new system applies to existing as well as new ICH Guidelines a history box has been added to the beginning of all Guidelines to explain how the Guideline was developed and what is the latest version.

With the new codification revisions to an ICH Guideline are shown as (R1), (R2), (R3) depending on the number of revisions. Annexes or Addenda to Guidelines have now been incorporated into the core Guidelines and are indicated as revisions to the core Guideline (e.g., R1).

For better comprehension of the E2B references within the text, please see below the document change history for E2B guideline.

E2B
Document History

First Codification	History	Date	New Codification **November 2005**
E2B	Approval by the Steering Committee under *Step 2* and release for public consultation.	1 May 1996	E2B
E2B	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	17 July 1997	E2B
E2B(M)	Approval of the first revision by the Steering Committee, without further consultation, under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	10 November 2000	E2B(R1)
E2B(M)	Approval by the Steering Committee of minor *Post-Step 4* editorial corrections *(second revision).	5 February 2001	E2B(R2)

Current *Step 2* version

E2B(R)	Approval of the third revision by the Steering Committee under *Step 2* and release for public consultation.	12 May 2005	E2B(R3)

This Q&A document provides conventions for the harmonized interpretation of the E2B guideline version 4.4.1 and the M2 specification document version 2.3. This will facilitate the implementation of the electronic transmission of Individual Case Safety Reports (ICSRs) in the three ICH regions.

Pharmaceutical companies, regulators and vendors were encouraged to submit implementation-related questions to the ICH E2B IWG.

Answers to these questions were developed by the ICH E2B IWG in accordance with the ICH consensus process.

Questions concerning the time frame and specific regional requirements currently not communicated in the E2B guidance are answered in guidance documents published for each region.

Questions requiring immediate answers should be addressed directly to the appropriate regional regulatory authority(ies).

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1 July 2003	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0001** During the period of transition, as Health Authorities or pharmaceutical companies migrate from paper to electronic ICSR submissions and exchanges using E2BM/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 1**: How can two or more exchanges of the same ICSR be linked together to avoid a duplicate report? **Question 2**: How can the current paper forms accommodate the full ICH format of the worldwide unique case identifier?	**Answer 1:** 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 organizations name should be 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 2:** 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.
2 July 2003	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0002** 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,	For the ICH E2BM 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 ;

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		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.	for MHLW: PTs.
3	July 2003	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0003*** What is the process to maintain, add, modify, or delete entries in the code lists in attachments 1 and 2 of E2BM?	Currently these lists cannot be modified.
4	July 2003	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0004*** 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?	There is currently no harmonised 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.
5	July 2003	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0005*** How can I send product-specific registration or other regulatory administrative information to multiple receivers in a single transmission?	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 E2BM. 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

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		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.
6 July 2003	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0007*** What language should I use for an ICSR transmission?	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
7 July 2003	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0008*** How can I submit a causality or scientific assessment in either an algorithmic or text representation in the current E2BM format?	The current structure of E2BM includes fields B.4.k.18.1-4, which allow the sender to indicate such assessments for each drug-event combination. Additionally, 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 are necessary.

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8	July 2003	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0009*** 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?	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). Additionally, field A.1.4 'Type of report' should be populated with a code of "4" (Not available to sender (unknown), if appropriate.
9	July 2003	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0010*** How can I identify the study name, study number, the patient, and the drug in clinical trials to be reported to the EU regulators and MHLW in the E2BM format?	The code list of 'Study type' in field A.2.3.3. is very short, so the type of study should be characterised 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 assure a unique patient identification. The trial drug identification is possible through the usual elements

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		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 E2BM allows for the distinction of unblinded vs. blinded information.
10 July 2003	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0011** There might be cases where, for one drug, and more than one formulation/dosage, lot number or indication are provided. How should this information be presented in the electronic transmission?	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.
11 July 2003	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0013** 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?	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.
12 Nov. 2003	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0015** Do the concepts of parent child reporting as described in the ICH E2B(M) guideline also apply to a foetus or an unborn child?	All reports affecting a foetus or an unborn child should be recorded as parent-child reports with the appropriate sections of E2B(M) completed.

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13	Nov. 2003	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0017** 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.	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.
14	Nov. 2003	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0018** What is the time frame for a drug to be included in the drug history section or as a concomitant drug?	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

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		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.

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15 Nov. 2003	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0019*** 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 organisation could get into legal problems.	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.
16 Nov. 2003 And Nov. 2004	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0022*** 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: Foetal distress and CS: One case on foetus (foetal distress), but none one the mother (CS). Follow-up on foetus: Event can be recoded to e.g., brain hypoxia: Outcome of event on foetus: 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.	**This answer was revised on 18 November 2004; the revision is indicated below in bolded text.** 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.

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		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.	Scenario 1: As the author of the question suggests, only one SAE report should be completed for the **foetus** ~~mother~~, with the AE of foetal 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 foetus should have a term for foetal 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.
17	Nov. 2003	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0026** *and* **E2BM IWG0037** Can you provide more detailed user guidance on the use of 'Term highlighted by the reporter' (B.2.i.3)?	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

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			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 EU and US but is mandatory in Japan for all complete case report types. For details, please consult MHLW guidance.
18	Nov. 2003	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0027*** When is it intended to introduce a repeatable indication section within the drug section?	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 Question # **10, E2BMIWG0011**).
19	Nov. 2003	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0028*** When is it intended to add the time zone information in M1.7 'Message date'?	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.

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			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.
20	Nov. 2003	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0029*** 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?	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.
21	Nov. 2003	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0031*** 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?	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

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22	Nov. 2003	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0034** 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.	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.
23	June 2004	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0037** A serious case was sent electronically by a company to a Regulatory Authority. Meanwhile, due to follow-up information received at the company, this case is now determined to be non-serious. (a) Should the company send a new message indicating that the case is now non-serious? (b) Should the company send a new message to nullify the case in the Regulatory Authority's database? (c) If the case becomes serious again, should the company send a new message with the same <safetyreportid>?	(a) Yes, the company should send a new message, updating the previous report with the new information, indicating that the case is now non-serious. The new information should be provided and, in addition, the fields below should be populated as follows: A.1.0.1: same identifier as in the initial report A.1.10.2: same identifier as in the initial report A.1.5.1: value = no A.1.7: date of receipt of the most recent information. (b) The company should not send a new message to nullify the

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		case in the Regulatory Authority's database.
		(c) Yes, this would be new information, and a follow-up report would be appropriate. The same identifiers A.1.0.1 and A.1.10.2 for the link to the initial ICSR should be used.
24 **June 2004**	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0038** In case of miscarriage: (a) Should an ICSR be prepared for the parent, the fetus, or both the parent and the fetus? (b) For the ICSR, should the seriousness criterion be "other medically important condition" rather than "result in death?" (c) Should the outcome of the parent's condition be entered in B.2.i.8 (outcome of reaction/event at the time of last observation)?	(a) See the answer to Question E2B(M) Q&A # 16 (b) Since the ICSR should be prepared only for the parent, the seriousness criterion is "other medically important condition." But, depending on the parent's condition, the seriousness criterion could be life-threatening and/or hospitalization. (c) Yes, the outcome of the parent's condition should be entered in B.2.i.8.
25 **June 2004**	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0040** How should field A.1.6 (the date report was first received from source) be populated, taking into consideration the recommendations of the ICH-E2D guideline: (a) Is it the date when the MAH receives a case report that fulfills minimum criteria for reporting? Or, the date when the sender receives the information that fulfills minimum criteria regardless of reportability from the primary source? (b) For example, what if the initial report was obtained on 01 May for the non-serious case and was not reported to the relevant regulatory	(a) Field A.1.6 should be populated with the date the information is received from the source. This information should fulfill the recommendations of the current ICH E2B(M)guideline, Section 1.5, "Minimum information" and the ICH E2D guideline, Section 4.2, "Minimum information for reporting." The minimum information for the transmission of a report should include at least one identifiable reporter (section A.2), identifiable patient (section B.1), one reaction/event (section B. 2), and one

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		agency; then on 10 May, what if follow-up information became available that necessitated expedited reporting because the case was determined to be serious and unlabeled?	suspect drug (section B.4). (b) In this example, in the field A.1.6, the initial report date and the follow-up report date are both 01 May. In the field A.1.7, the most recent information available date is 01 May for the initial report and 10 May for the follow-up report. Whether or not this case safety report should be reported to the relevant regulatory authority will depend on the local authorities.
26	June 2004	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0042*** What is the difference between releases 1.0 and 2.0 of the v2.1 DTD? Is either one acceptable for use?	Release 1.0 of v2.1 DTD had errors that were corrected, which resulted in release 2.0 of v2.1 DTD. Release 1.0 should not be used. Release 2.0 should be used.
27	Nov. 2004	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0046*** Case A is linked with Case B. When case B is transmitted in E2B format, should A.1.12 field in the file contain A.1.0.1 Safety Report Id or A.1.10 Company Number for case A?	When a case report A is to be linked to case report B by a company X, the field A.1.12 of both reports should be populated. In case report A the field A.1.12 should capture the value of the field A.1.10.1 (if the sender is a regulator) or A.1.10.2 (if the sender is a company) as the field appears in case report B. Similarly, in case report B, the field A.1.12 should capture the value of the field A.1.10.1 (if the sender is a regulator) or A.1.10.2 (if the sender is a company) as the field appears in case report A.

E2B Questions and Answers (R5)

Date of Approval		Questions	Answers
28	Nov. 2004	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0047*** A man started medications before his partner became pregnant. But she has a miscarriage now. (a) Is the ADR a miscarriage? (b) Is the patient of the report the father or mother? (c) Is the route of administration how the father took the medicine?	(a) Yes. In this case the ADR should be the miscarriage experienced by the mother. (b) The patient should be the mother. Per the user guidance, in case of fetal demise or early spontaneous abortion, only a parent report is applicable. The sections B.1.1 to B.1.8 should be completed. (c) Yes. The route of administration should be how the father was given the suspect medication. But while the characteristics of the suspect drug should be captured in section B.4, it should be clearly mentioned in field B.4.k.19 (additional information on drug) that the suspect medication was taken by the father. Since it's a mother's report, the route of administration (B.4.k.8.) should be indicated as unknown.
29	Nov. 2004	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0048*** A man started medications before his partner became pregnant. The baby was born with ADR. Are the following statements correct? (a) A report should be submitted as a parent-child/fetus report. (b) B.1.10 captures the data of the father. (c) Route of administration is unknown.	(a) Yes. The report should be submitted as a parent-child/fetus report. The patient should be the baby. (b) Yes, B.1.10 should be populated with the father's data. (c) Yes, in this case, not enough information was provided to determine the route of administration of the suspected drug to the baby. The route of administration should be indicated as unknown.

E2B Questions and Answers (R5)

Date of Approval	Questions	Answers
30 Nov. 2004	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0050** Given the user guidance in the E2BM guideline and question # **10 (E2BM IWG 0011)** in the Q&A document, please describe the preferred use of B.4.k.15a for the following two scenarios. The reports are from spontaneous sources and exact dates of drug administration are unknown in both instances: Scenario 1: Identifiable patient received drug "X" p.o. in hospital for one week and then the same drug/form/dose for two weeks at home. There was a serious, unexpected event and an identifiable reporter, etc. (a) For scenario 1, would it be necessary to repeat B.4.k.15a? That is, should a single entry of <3> populate the duration field (B.4.k.15b units entry <803> week) or should the related field repeat with the drug listed twice with <1> and <2> populating the corresponding B.4.k.15a field, respectively? Scenario 2: Identifiable patient received drug "X" i.v. in hospital for one week and then took the same dose but a different formulation of the same drug/dose p.o. for two weeks at home. There was a serious, unexpected event and an identifiable reporter, etc. (b) For scenario 2, would B.4.k.15a repeat? That is, should a single entry of <3> populate the duration field or would it be preferable to show the two formulations separately and with two separate entries in the respective duration fields, <1> and <2> for the i.v. and p.o. form/administration? (c) Should, for Scenario 2, the drug be listed twice (different forms, per	(a) For scenario 1, if the drug treatment was continuous, drug "X" should be listed in B.4.k.2 (B.4.k.2.1, Proprietary medicinal product name, and B.4.k.2.2, Active drug substance name) with <3> populating field B.4.k.15a (Duration of drug administration) and <803> (week) populating field B.4.k.15b (Duration of drug administration unit). Fields B.4.k.15a and B.4.k.15b would not need to be repeated. However, if treatment was stopped between hospital and home, it would be preferred to repeat drug "X" in block B.4.k.2 (repeat entries in both field B.4.k.2.1 and field B.4.k.2.2), with values of <1> and <2> populating the corresponding duration fields (B.4.k.15a) and <803> (week) populating the two unit fields (B.4.k.15b). (b) For scenario 2, drug "X" should be listed twice in the repeating block B.4.k.2 with values of <1> and <2> populating the two corresponding duration fields (B.4.k.15a) and <803> populating both of the units fields (B.4.k.15b). The two routes of administration can be indicated by providing separate entries of <042> (Intravenous not otherwise specified) and <048> (Oral) in the corrresponding B.4.k.8 fields (Route of administration). (c) For Scenario 2, a duration value of <3> in field B.4.k.15a would not be considered appropriate.

E2B Questions and Answers (R5)

Date of Approval	Questions	Answers
	Q&A 10) and the duration for BOTH show as 3? (d) Should an adjustment be made in the E2B message if there was a known missed dose/day or two in either scenario (to cover the "intermittent" user guidance)?	(d) An adjustment in the structured data fields need not be made for a known missed dose/day or two in either scenario (in accordance with the "intermittent" user guidance); descriptive information can be provided in the dosage text field (B.4.k.6).
31 Nov. 2004	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0051*** ICH E2D states: For regulatory purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction. (a) In the case of a spontaneous report with an unstated relationship, does that imply that the fields B.4.k.18.1 through B.4.k.18.4 should be populated with the causality assessment "possible" for all the drugs? (b) Can the company have a different opinion from the reporter and state the causality with the same drug is unrelated or unlikely?	(a) If an event is spontaneously reported to a company about the patient who took that company's drug, and the relationship is unstated, it implies a suspected causal relationship to the drug. However, fields B.4.k.18.1 through B.4.k.18.4 should be left blank unless otherwise required by local regulation. (b) The company's causality assessment can be captured in fields B.4.k.18.1 through B.4.k.18.4 and the sender's comments can be captured in field B.5.4.
32 Nov. 2004	*Question generated by the E2B Implementation Working Group :* ***E2BM IWG0053*** A company wishes to report a fixed combination medicinal product (e.g., ace inhibitor 20 mg and diuretic 12.5 mg). How should we code this information in section B.4, taking into account the need to provide the structured dosage information for this combination?	The proprietary medicinal product name of the fixed combination product should be entered in B.4.k.2.1. The active substance for the ace inhibitor should be entered in B.4.k.2.2. B.4.k.2.2 should be repeated and the active substance for the diuretic should be repeated. The dosage information should be entered in B.4.k.6 as free text. In Japan, codes are available for approved combination drugs and

E2B Questions and Answers (R5)

Date of Approval		Questions	Answers
			can be used in the appropriate fields: B.4.k.2.1 (proprietary medicinal product name) and B.4.k.2.2 (active substance name).
33	Nov. 2004	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0054** If a report is forwarded to a company by a Health Authority, should the company consider that: (a) the Health Authority's causality assessment is at least "possible"? (b) the reporter's causality assessment is also at least "possible"?	(a) and (b) By definition a spontaneous report contains suspected adverse reactions (i.e., a possible causal relationship is suspected but not established). However, there is no universally accepted definition for "possible" in the scale of causality assessment. It is therefore not possible to provide a precise answer to this question. It is up to the company and receiver to define causality assessment method and classify the case-reports accordingly.
34	Nov. 2004	*Question generated by the E2B Implementation Working Group :* **E2BM IWG0055** Use of Elements: -- B.4.k.5.3 <drugseparatedosagenumb> -- B.4.k.5.4 <drugintervaldosageunitnumb> -- B.4.k.5.5 <drugintervaldosagedefinition> Can you confirm that it is the case that if any one of the above three elements is provided then all three must be provided, as sending only some of these elements gives information that cannot be interpreted?	To provide structured information in B.4.k.5 (Structured dosage information), the information should be provided in the relevant fields. However, if the data are incomplete or difficult to structure, the available information should be provided in B.4.k.6 (Dosage text).