ICH E2B(R3) Expert Working Group / Implementation Working Group
ICH E2B(R3) Guideline: Electronic Transmission of Individual Case Safety Reports (ICSRs)

Questions and Answers

Version 2.4

17 January 2023

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

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In order to facilitate the implementation of the E2B(R3) Guideline, the ICH Experts have developed a series of Q&As:

E2B(R3) Q&As
Document History

Code	History	Date
E2B(R3) Q&As Version 1.0	Approval by the ICH Steering Committee under *Step 4*	12 November 2014
E2B(R3) Q&As Version 1.1	Approval by the ICH Assembly under *Step 4*	16 June 2016
E2B(R3) Q&As Version 2.0	Approval by the ICH Assembly under *Step 4*	10 November 2016
E2B(R3) Q&As Version 2.1	Approval by the ICH Assembly under *Step 4*	1 June 2017
E2B(R3) Q&As Version 2.2	Approval by the ICH Assembly under *Step 4*	7 June 2018
E2B(R3) Q&As Version 2.3	Approval by the ICH Assembly under *Step 4*	6 June 2019
E2B(R3) Q&As Version 2.4	Approval by the ICH Assembly under *Step 4*	17 January 2023

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PREFACE

This Q&A document provides clarifications for the harmonized interpretation of the E2B(R3) IG package and should be reviewed in conjunction with the IG package. This will facilitate the implementation of the electronic transmission of Individual Case Safety Reports (ICSRs) in the ICH regions. The sections of this Q&A document corresponds to the organization of the E2B(R3) IG.

Pharmaceutical companies, regulators and vendors are encouraged to submit implementation-related questions to the ICH E2B(R3) EWG/IWG; answers to these questions are developed by the ICH E2B(R3) EWG/IWG in accordance with the ICH consensus process.

Questions concerning the time frame and specific regional requirements not communicated in the E2B(R3) guidance are answered in guidance documents published for each region.

The use of the terminology “upgrading” or “downgrading” in the documents included in the IG package refers to the technical conversion between E2B(R2) and E2B(R3).

Future update to this Q&A document, if any, will be published at ICH web site.

E2B(R3) Questions and Answers

1. Purposes

No Q&A

2. Background

No Q&A

3. Essential Components

# (# from ver.1.1)	Date of Approval	Questions	Answers	E2B(R3) Data Element
3.1 (001)	**November 2014**	Does ICH data type "AN" accept Space? Does ICH data type "AN" accept all characters listed in UTF8?	In principle, ICH "AN" data type accepts all characters, including space and some special characters listed in UTF8, but some characters such as > and < are not allowed with XML message. So please refer to section 3.6 of the ICH ICSR Implementation Guide for further clarification. However, ICH data elements with the ICH "AN" data type may not always have a one-to-one mapping with the data type in ISO/HL7 27953-2 ICSR message standard. The representation of the data can vary across implementations. For Example ICH F.r.4 Normal Low Value and ICH F.r.5 Normal high Value. These data elements specify use of the ICH AN data type; however, the ISO/HL7 27953-2 message specification restricts allowable XML schema values using the HL7 xsi:type code designation Physical Quantity (PQ). The HL7 PQ data type is expressed as two XML schema attributes: value and unit; value has HL7 REAL data type and units are expressed as UCUM codes. For the use and information of the HL7 data type, please refer to the ISO/HL7 27953-2 Informative Annex F: *HL7 Data Type Specification*. In the Business Rule section for the related data elements, the ICH ICSR Implementation Guide provides information and examples for representing the ICH AN data type with HL7 data type in transmission.	
3.2 (002)	**November 2014**	Is it possible to use NI even if NI is not listed in allowed values? Because, the explanation of NI is that No information whatsoever can be inferred from this exceptional value. This is the most	No, only nullFlavors specified for each element in IG and Q&A document are acceptable. The value set of nullFlavor in Q&A supersede the value set stated in the IG.	

		general exceptional value. It is also the default exceptional value.		
3.3 (004)	**November 2014**	Does XML schema define default values for some attributes?	The ISO/HL7 schema files automatically populate certain attributes with a default value, such as unit='1' for PQ data type and mediaType='text/plain' for ED data type. The ICSR sender should replace the default value with an appropriate value pertaining to the data being transmitted. For example, use the appropriate UCUM code for representing a unit of measurement for physical quantities (PQ) and media designation for encapsulated data (ED). To help reduce parsing errors, the sender should omit optional data element tags if there is no information to be transmitted. For example, patient age is an optional data element and the sender should omit the entire age observation class if no age value is known.	
3.4 (005)	**November 2014**	Is there anything senders should consider in creating XML files for ICSRs?	Senders should refer not only to the ICH Implementation Guide and regional Implementation Guides but also its Appendices such as Reference instances, Technical Information and so on.	
3.5 (007)	**November 2014**	There is no guidance whether case sensitive form or case insensitive form should be used for codes in the ICH E2B(R3) ICSR messages.	In the ICH E2B(R3) ICSR messages, case sensitive form should be used for codes. Please refer to regional guidance for more information about case sensitivity.	
3.6 (008)	**November 2014**	Use of HL7 nullFlavors requires implementation of very specific business rules for parsing – not necessarily as part of ICSR file validation. ICSR file validation is checking appropriate HL7 nullFlavors by data element (datatype). Backend system parsing rules are different because they affect how data is actually displayed / queried in the database: EX: Date fields with a NI value cannot be parsed to a field structured for date/time.	Support for HL7 nullFlavor values, such as MSK (masked), NI (No Information) and UNK (Unknown) may vary across implementation. Systems should be designed to receive process and re-produce a compliant message utilizing nullFlavors as defined in the ICH E2B(R3) IG.	
3.7 (010)	**November 2014**	A serious case was sent electronically by a company to a Regulatory Authority. Meanwhile, due to follow-up information received at the	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.	

		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 safety report identifier?	b) No, the company should not send a new message to nullify the case in the Regulatory Authority's database. c) Yes, this would be new information, and a follow-up report would be appropriate utilizing the same safety report identifier.	
3.8 (011)	**November 2014**	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.	
3.9 (028)	**June 2016**	In the ISO 639-2 language code list some languages appear twice with two different codes designated B and T: for instance Czech is either cze (B) or ces (T) where 'B' indicates 'bibliographic' and 'T' indicates 'terminology'. In such instances is one of these correct (meaning that the other is incorrect) – if so, which, or is either OK?	For those languages where (T) and (B) codes are provided the (T) code should be used in E2B(R3) messages.	
3.10 (029)	**June 2016**	Does data length provided in the IG (e.g. 5AN) represent data length (byte) or apparent number of characters? In UTF-8, surrogate pairs and combining characters have longer data length (byte) than their apparent data length.	Data length provided in the IG represents the apparent number of characters. Please note some languages/characters require more than a single byte for a character.	

3.11 (038)	**June 2016**	ISO 3166 Part 1 (alpha-2) country codes are provided in the ISO web site. https://www.iso.org/obp/ui/#home There are some categories like "Officially assigned codes" or "Other code types". Does ICH accept "Officially assigned codes" only? Note: "EU" is categorized in "exceptionally reserved"	IG specifies use of ISO 3166 Part 1 (alpha-2). ISO 3166 Part 1 (alpha-2) supports use of country codes in E2B(R3) messages. This includes "Officially assigned" country codes plus "EU" in the "Exceptionally reserved" category. The "Unassigned" category should not be used. "Transitionally reserved", "Indeterminately reserved" and "Formerly used" categories may be used when appropriate, e.g., for legacy data.	N, C to H
3.12	**June 2018**	To use UCUM in E2B(R3), is it required to use a UCUM syntax checking tool in order to ensure that units of measurements are correctly formed?	ICH E2B(R3) standard does not require any UCUM syntax checking tools.	
3.13	**June 2019**	As a regulator, how does one request an ICH Object Identifier (OID) assigned to a region?	ICH M2 is responsible for assigning OID in the ICH name space to the ICH regulators. An information paper about OID can be found at the ESTRI website, Recommendations page: http://estri.ich.org/recommendations/index.htm Please contact M2 via ICH Secretariat at admin@ich.org to request OID assignment.	

4. ICH E2B(R3) DATA ELEMENTS

# (# from ver.1.1)	Date of Approval	Questions	Answers	E2B(R3) Data Element

<table>
<tr>
<td>4.1
(009)</td>
<td>November 2014</td>
<td>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?

Is the route of administration how the father took the medicine?</td>
<td>Following are abbreviated answer for the question and examples for various scenario regarding parent and/or child/foetus.
a) Yes. In this case the ADR should be the miscarriage experienced by the mother.

b) The patient should be the mother.

c) Yes. The route of administration should be how the father was given the suspect medication.

Scenario 1: Miscarriage, drug administered to Mother
<table>
<tr><td>Patient (D)</td><td>Mother</td></tr>
<tr><td>AE (E)</td><td>Miscarriage</td></tr>
<tr><td>Drug section (G)</td><td>Product taken by mother</td></tr>
<tr><td>Route of Administration (G.k.4.r.10)</td><td>Route administered to mother</td></tr>
</table>
Scenario 2: Miscarriage, drug administered to Father
<table>
<tr><td>Patient (D)</td><td>Mother</td></tr>
<tr><td>AE (E)</td><td>Miscarriage</td></tr>
<tr><td>Drug section (G)</td><td>Product taken by father</td></tr>
<tr><td>Route of Administration (G.k.4.r.10)</td><td>Use nullFlavor “UNK” in G.k.4.r.10.1
Describe information about father and mother in the narrative</td></tr>
<tr><td>Additional Information on Drug (G.k.10.r)</td><td>3 (Drug taken by the father)</td></tr>
</table>
Scenario 3: foetus or breast-feeding infant is exposed to drug(s) through the mother and experienced adverse events/reactions
<table>
<tr><td>Patient (D)</td><td>Infant/foetus</td></tr>
<tr><td>AE (E)</td><td>AE experienced by Infant/foetus</td></tr>
<tr><td>Drug section (G)</td><td>Product taken by mother</td></tr>
<tr><td>Route of Administration (G.k.4.r.10)</td><td>This is usually an indirect exposure, such as transmammary</td></tr>
</table>
</td>
<td>C.1.1,
C.2.r.3,
D,
E.i.9</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>Parent Route of Administration (G.k.4.r.11)</td><td>Route administered to mother</td></tr>
<tr><td>For a Parent-child / Foetus Report, Information Concerning the Parent (D.10)</td><td>Mother’s information according to the user guidance for section D</td></tr>
</table>
Scenario 4: child/foetus experienced adverse events/reactions through drug(s) administered to father
<table>
<tr><td>Patient (D)</td><td>Child/foetus</td></tr>
<tr><td>AE (E)</td><td>AE experienced by child/foetus</td></tr>
<tr><td>Drug section (G)</td><td>Product taken by father</td></tr>
<tr><td>Route of admin (G.k.4.r.10)</td><td>Use nullFlavor “UNK” in G.k.4.r.10.1
Describe information about father and mother in the narrative</td></tr>
<tr><td>Parent Route of Administration (G.k.4.r.11)</td><td>Route administered to father</td></tr>
<tr><td>Additional Information on Drug (G.k.10.r)</td><td>3 (Drug taken by the father)</td></tr>
<tr><td>For a Parent-child / Foetus Report, Information Concerning the Parent (D.10)</td><td>Father’s information according to the user guidance for section D</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>4.2 (014)</td>
<td>November 2014</td>
<td>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?</td>
<td>If no information on the primary source is available, section C.2.r should identify the Health Authority as the primary source.
Field C.2.r.4 ‘Qualification’ should be populated with nullFlavor “UNK”.
Additionally, field C.1.3 ‘Type of report’ may be populated with a code of “4” (Not available to sender (unknown), if appropriate.</td>
<td>C.1.3, C.2.r</td>
</tr>
</table>

<table>
<tr>
<td>4.3
(015)</td>
<td>November 2014</td>
<td>The conformance of C.1.5 is “Required”. Even if a sender has only first received information and no follow-up information, must a sender enter date in this field?</td>
<td>Yes, a sender must enter date.
If a sender has only first received information, the date of first received information and the date of most recent information are same, so a sender enters the date correspond to C.1.4 in C.1.5.</td>
<td>C.1.4,
C.1.5</td>
</tr>
<tr>
<td>4.4
(019)</td>
<td>November 2014</td>
<td>About E2B(R3) data element: E.i.3.2 Seriousness Criteria at Event Level,

a) How to describe “unknown” and “not serious”? What is allowed value for this data element?

b) How to describe allowed values and "left blank" in XML?</td>
<td>a) E.i.3.2 are mandatory elements and False is not a value allowed for this data element. This mandatory data element should either be ‘true’ or nullFlavor= ‘NI’.
When the information is unknown or the event is not serious, “NI” should be populated.

b) “Left blank” if not serious using the null flavor “NI”.
All 6 criteria in E.i.3.2 should be included in XML every time (even if a report is non serious).
The following is an XML example.
<value xsi:type="BL" nullFlavor=”NI” /></td>
<td>E.i.3.2</td>
</tr>
<tr>
<td>4.5
(020)</td>
<td>November 2014</td>
<td>Here is scenario on E.i.4 and E.i.5:
<table>
<tr><td>Reaction Sequence</td><td>E.i.4 Start date</td><td>E.i.5 End date</td></tr>
<tr><td>Reaction1</td><td>01-Feb-2010</td><td>02-Feb-2010</td></tr>
<tr><td>Reaction2</td><td>03-Feb-2010</td><td>-</td></tr>
<tr><td>Reaction3</td><td>-</td><td>01-Jan-2010</td></tr>
</table>
How to get the blank start date and end date details. As per the IG, if we have to consider start date of first reaction and end date of last reaction, the output will not be correct.</td>
<td>Senders should populate the most accurate information known for each event. A blank field for start date or end date or both is acceptable if the information is not known to the sender. When a precise date is not available, the decision of whether to leave blank or an inferred date for a given event should be left up to the sender’s clinical judgment. If the events are thought to be related (i.e., if event1 is a sign or symptom of event2), it would be clinically reasonable to use the earliest start date or latest end date, as relevant, for both events. However, a sender should not infer dates unless there is a clear clinical rationale and this rationale should be stated in the case narrative.</td>
<td>E.i.4,
E.i.5</td>
</tr>
<tr>
<td>4.6
(022)</td>
<td>November 2014</td>
<td>How are the NullFlavors ‘NINF’ and ‘PINF’ implemented in ICH E2B(R3)?</td>
<td>When empty data elements are transmitted, NullFlavors are used to code the reason for the lack of data in a standardized manner. This allows for the creation of valid messages containing mandatory elements without transmitting content.
For ICH E2B(R3), the NullFlavors ‘NINF’ (negative infinity of numbers) and ‘PINF’ (positive infinity of numbers) are used only for the data element ICH E2B(R3) F.r.3.2 Test Result, and only when the element describes a range (e.g. data type IVL<…>) with an (unknown) infinity.
For example, the concept of ‘equal or greater to 3’ can be represented as</td>
<td>F.r.3.2</td>
</tr>
</table>

			the range from '3' to 'positive infinity', e.g. *any* (unknown) number greater than 3.	
4.7 (023)	**November 2014**	User Guidance of F.r.3.2 Test Result (value/qualifier) in the IG ver. 5.01 states that "A qualifier symbol can be added to the value when appropriate. The supported qualifiers are 'greater than', 'less than', 'greater than or equal to' and 'less than or equal to'". However allowed values are Numeric and null flavor (NINF and PINF). Can senders add a qualifier symbol (<, >, ≤, ≥)?	No, senders cannot add a qualifier symbol in this data element. This data element captures the value (amount) for the test result. In ICSR message, this data element is represented in HL7 IVL_PQ data type which is a composite data type with multiple attributes. "Positive Infinity (PINF)" and "Negative Infinity (NINF)" null flavors are used to express "Greater than" and "Less than" a specific value respectively. Followings are examples for test results with exact value, greater or less than a specific value. Test Result = 10 (mg/dl) <value xsi:type="**IVL_PQ**"> Test Result < 10 (mg/dl) <value xsi:type="**IVL_PQ**"> <low nullFlavor="**NINF**"/><high value="**10**" unit="**mg/dl**" inclusive="**false**"/></value> Test Result <= 10 (mg/dl) <value xsi:type="**IVL_PQ**"> <low nullFlavor="**NINF**"/><high value="**10**" unit="**mg/dl**" inclusive="**true**"/></value> Test Result > 10 (mg/dl) <value xsi:type="**IVL_PQ**"> <low value="**10**" unit="**mg/dl**" inclusive="**false**"/><high nullFlavor="**PINF**"/></value> Test Result >= 10 (mg/dl) <value xsi:type="**IVL_PQ**"> <low value="**10**" unit="**mg/dl**" inclusive="**true**"/><high nullFlavor="**PINF**"/></value> The IG was updated to remove the references to qualifiers symbols. The correction is reflected to the IG version 5.02 (modified in November 2016).	F.r.3.2

4.8 (024)	**November 2014**	If a value of test results does not have a suitable UCUM code or a unit (for example International Normalized Ratio, INR) or a unit of test results is unknown, how should the test results be entered?	In such case, senders should enter the value and unit as unstructured data in F.r.3.4.	F.r.3.4
4.9 (026)	**November 2014**	a) How should re-administration data be entered after recovery from AE, e.g., G.k.4.r.8 or G.k.4.r repetition? b) When multiple dosage information (G.k.4.r) is available for a drug, which dosage information should be used for G.k.8? c) Is it possible to identify the re-administration after drug is discontinued or after drug is temporarily stopped?	Answers to question a) through c) are summarized into the scenarios below: The data element (G.k.8) is not a repeatable data element and captures the action taken with the *suspect* drug as a result of the reaction(s) / event(s) as provided by the reporter of the information. This data element is a within the 'parent' instance of **G.k Drug** and only one action can be captured for each instance of **G.k Drug.** Because this data element is not associated with its own 'time' element, the relevant 'time' for **G.k.8 Action(s) Taken with Drug** is the onset of the reaction. Analysis of the dosage information records in G.k.4 in combination with start date of the reaction/event in **E.i.4 – Date of Start of the Reaction/Event** – would enable the receiver of the information to determine the relevant **G.k.4 Dosage Information** record associated with the reaction(s)/event(s). The information related to the outcome of the reaction(s)/event(s) is noted in **E.i.7 - Outcome of Reaction / Event at the Time of Last Observation**. If the reaction(s)/event(s) do not recur after reintroducing the drug**, G.k.9.i.4 Did Reaction Recur on Re-administration?** would be set to 2 (rechallenge was done, reaction did not recur) and **E.i.7 – Outcome of Reaction / Event at the Time of Last Observation** would be set to 1 = recovered/resolved. An example is provided in Appendix A.	E.i.4, E.i.7, G.k.4.r, G.k.8, G.k.9.i.4
4.10 (027)	**November 2014**	Clarification was requested for usage on coding reports of possible counterfeit drugs.	"1" should be selected for both suspected and confirmed counterfeit products in G.k.10.r and the appropriate MedDRA term should be selected for E.i.2.1b. Any explanatory information should be included in case narrative. If new information is received to confirm the product is not a counterfeit, then G.k.10.r should be changed appropriately as follow up. If the product is confirmed as a counterfeit, the sender should use the appropriate MedDRA code in H.3.r and explain in narrative.	E.i.2.1b, G.k.10.r, H.1, H.3.r

4.11 (030)	**June 2016**	When retransmitting an ICSR received from another sender such as a regulatory authority, partner company, or other source, which reporter should be marked as 'Primary Source for Regulatory Purposes' (field C.2.r.5)?	As mentioned in the E2B(R3) implementation guide, the primary source of the information is the person who provided the facts about the ICSR. In case of multiple sources, the 'Primary Source for Regulatory Purposes' (C.2.r.5) is the person who first reported the facts to the original sender, not retransmitter. The primary source should be distinguished from senders and retransmitters. Information on the sender and retransmitters is captured in section C.3. When retransmitting an electronic ICSR received from another sender, such as a regulatory authority, partner company, or other source in E2B format, the Primary Source information in the initial transmission should reflect the reporter with first-hand information on the case and this should not be changed. The reporter identified as 'Primary Source for Regulatory Purposes' in the original transmission should remain unchanged in all subsequent retransmission of the case.	C.2.r.5, C.3
4.12 (032)	**June 2016**	Which data element (F.r.3.4 Result unstructured data or F.r.6 Comments) is applicable for test results such as comments on CT, MRI, or radiogram?	Field F.r.6 is reserved for comments made by the reporter about the results of tests and procedures. Unstructured findings from tests and procedures such as CT, MRI, radiogram, etc. should be provided as free text in field F.r.3.4.	F.r.3.4, F.r.6
4.13 (033)	**June 2016**	The mother's drug exposure has started prior to her pregnancy. Is "G.k.6 Gestation period at time of exposure" necessary to be populated on the child/foetus report and/or mother report?	It is appropriate to use G.k.6 to capture the earliest exposure during pregnancy, a clinical judgment should be used to choose the most appropriate value/unit.	G.k.6
4.14 (034)	**June 2016**	Is "D.2.2.1 Gestation Period When Reaction/Event Was Observed in the Foetus" necessary in the foetus report when drug was taken by father?	In a foetus report, regardless the exposure from father or mother, the foetus age information should be provided in D.2.2.1. Information concerning the parent should be provided in section D.10.	D.2.2.1, D.10
4.15 (035)	**June 2016**	What is an appropriate age for newborn if an adverse drug reaction/event has been developed during pregnancy but just observed at time of delivery?	Section D.2 provides several options for reporting patient age information. The sender should select the most appropriate field based on the information provided. Based on the information provided in the question, field D.2.3 may be the most appropriate field to report the patient age.	D.2

4.16 (036)	**June 2016**	What is an appropriate value for "G.k.9.i.4 Did reaction recur on re-administration?" if adverse drug reaction/event on re-administration is not exactly the same as the one on previous administration? Ex) E.i.2.1 Reaction/event: liver disorder Re-administration: Aspartate aminotransferase increased	Medical judgment should be used to assess the conceptual similarity of the events. MedDRA codes do not need to be identical. [Refer to the most recent ICH MedDRA Term Selection: Points To Consider.]	E.i.2.1, G.k.9.i.4
4.17	**November 2016**	Certain units that are commonly used to express concentration or strength of pharmaceutical products are included in the UCUM Mass Concentration Units but are missing from the E2B constrained term list. An example is mg/mL that might be used in E2B(R3) data element G.k.2.3.r.2b Strength (unit). Is it possible to add mg/mL to the terms available for strength units in ICSR XML messages?	The unit "mg/mL" is now available on the constrained E2B Code List #25 (file name E2B CL25 ich-dose-strength-unit.xml). The IWG will evaluate other UCUM units, singly and in combination, for possible inclusion in the E2B constrained units list.	G.k.2.3.r.2b
4.18	**June 2017**	How should "Decade" be represented in data element D.2.2b Age at Time of Onset of Reaction / Event (unit) and D.10.2.2b Age of Parent (unit)? There is a discrepancy between the IG Value allowed and the code list #26, which one should be used?	{Decade} in the IG should not be used. E2B(R3) EWG/IWG consulted with UCUM and preferred notation is "10.a". The code list #26 has been updated accordingly.	D.2.2b D.10.2.2b
4.19	**June 2018**	The data elements, F.r.4 Normal Low Value and F.r.5 Normal high Value, specify use of the ICH AN data type. However, an error is occurred by some alphanumeric characters entered in these data elements. Is it possible to enter alphanumeric characters in these data elements?	While IG indicates data type 50AN and Value Allowed free text, value should be transmitted as two XML attributes: value and unit. Use only numeric data in value and alphanumeric in unit as currently documented in the Business Rule(s) section of data elements F.r.4 and F.r.5.	F.r.4, F.r.5

<table>
<tr><td>4.20</td><td>June 2018</td><td>Please clarify which nullFlavour is allowed for data element D.6 ‘last menstrual period’. The data element description for D.6 allows only ‘MSK’ as a nullFlavor. But the table of definitions for nullFlavors (IG section 3.3.6) provides the following example for the value ‘NA’: last menstrual period for a male’.</td><td>Only MSK is allowed nullFlavor for D.6.</td><td>D.6</td></tr>
<tr><td>4.21</td><td>June 2018</td><td>Please clarify the conformance of data element F.r.3.4.</td><td>Optional, but required when all the following conditions are met:
<table><tr><td>F.r.2 – Test Name</td><td>Populated</td></tr><tr><td>F.r.3.1 – Test Result (code)</td><td>Not populated</td></tr><tr><td>F.r.3.2 – Test Result (value / qualifier)</td><td>Not populated</td></tr><tr><td>F.r.3.3 – Test Result (unit)</td><td>Not populated</td></tr></table></td><td>F.r.3.4</td></tr>
<tr><td>4.22</td><td>June 2019</td><td>There is inconsistency regarding a data entry rule between ICH OID and Business Rule(s) of D.1.1.1 – D.1.1.4. For example, the ICH OID of D.1.1.4 specifies the ICH code list #4 and the numeric code "4" should be entered according to the list. However, the Business Rule(s) of D.1.1.4 is described as <code code = "investigation" codeSystem = "2.16.840.1.113883.3.989.2.1.1.4"/> . This looks as if a sender is required to enter a kind of word, and not a numeric code. Which way of data entry is appropriate for these data elements?</td><td>A numeric code listed in the ICH code list #4 is required to be entered for D.1.1.1 – D.1.1.4. For further information, refer the X-path described in Appendix I(G) Technical Information version 1.02 and Reference Instances version 3.1.</td><td>D.1.1.1 – D.1.1.4</td></tr>
</table>

<table>
<tr>
<td>4.23</td>
<td>January 2023</td>
<td>For vaccines given according to a schedule of multiple doses, how should the ICSR message capture which dose (sequence number) in the schedule that was given?</td>
<td>Information on the suspected dose schedule (sequence number) should be recorded in G.k.4.r.8 Dosage Text with alpha-numerical values.
E.g., 1st dose, Dose #2, Dose no. in series: 3, etc.

Information concerning unsuspected dose schedule should be recorded in D.8.r Relevant Past Drug History.
When information regarding past doses is unavailable, only the information concerning the suspected dose should be recorded.
Please refer to regional guidance for more information about vaccine reporting.

Scenario 1: Patient received two doses of the same or different vaccine(s), the first dose is not suspected and the second dose is suspected
<table>
<tr><th>Data element</th><th>k/r</th><th>Value</th></tr>
<tr><td>Characterization of Drug Role (G.k.1)</td><td>k=1</td><td>1 (Suspect)</td></tr>
<tr><td>Drug Identification (G.k.2)</td><td>k=1</td><td>Second vaccine</td></tr>
<tr><td>Dosage and Relevant Information (G.k.4.r)</td><td>k=1</td><td>Information related second vaccine</td></tr>
<tr><td>Dosage Text (G.k.4.r.8)</td><td>k=1</td><td>E.g. 2nd dose</td></tr>
<tr><td>Relevant Past Drug History (D.8.r)</td><td></td><td>First vaccine</td></tr>
</table>
Scenario 2: Patient received two doses of the same vaccine and both doses are suspected
<table>
<tr><th>Data element</th><th>k/r</th><th>Value</th></tr>
<tr><td>Characterization of Drug Role (G.k.1)</td><td>k=1</td><td>1 (Suspect)</td></tr>
<tr><td>Drug Identification (G.k.2)</td><td>k=1</td><td>First and second vaccine</td></tr>
<tr><td>Dosage and Relevant Information (G.k.4.r)</td><td>k=1
r=1</td><td>Information related first vaccine</td></tr>
<tr><td>Dosage Text (G.k.4.r.8)</td><td>k=1
r=1</td><td>E.g. 1st dose</td></tr>
<tr><td>Dosage and Relevant</td><td>k=1</td><td>Information related second</td></tr>
</table>
</td>
<td>D.8.r
G.k.1
G.k.2
G.k.4.r
G.k.4.r.8</td>
</tr>
</table>

Information (G.k.4.r)	r=2	vaccine
Dosage Text (G.k.4.r.8)	k=1 r=2	E.g. 2nd dose

Scenario 3: Patient received two doses of different vaccines and both doses are suspected

Data element	k/r	Value
Characterization of Drug Role (G.k.1)	k=1	1 (Suspect)
Drug Identification (G.k.2)	k=1	First vaccine
Dosage and Relevant Information (G.k.4.r)	k=1	Information related first vaccine
Dosage Text (G.k.4.r.8)	k=1	E.g. 1st dose
Characterization of Drug Role (G.k.1)	k=2	1 (Suspect)
Drug Identification (G.k.2)	k=2	Second vaccine
Dosage and Relevant Information (G.k.4.r)	k=2	Information related second vaccine
Dosage Text (G.k.4.r.8)	k=2	E.g. 2nd dose

5. DOCUMENT ATTACHMENT

# (# from ver.1.1)	Date of Approval	Questions	Answers	E2B(R3) Data Element
5.1 (037)	**June 2016**	The codesystem versions for the E2B code lists used in the ICH E2B(R3) reference instances are old compared to the latest version of the E2B code lists. Should a sender update the codesystem version appropriately?	Yes, a sender should update the codesystem version in ICSR messages (xml files) for submission. Acceptable codesystem version(s) are designated by regulatory authorities in each region.	

6. THE ICSR ACKNOWLEDGEMENT TRANSACTION

No Q&A.

7. APPENDICES

# (# from ver.1.1)	Date of Approval	Questions	Answers	E2B(R3) Data Element
7.1	**June 2017**	If date/time is provided without timezone offset can I assume that it is UTC time?	No, do not make this assumption. If date/time is provided as UTC exactly it would be expressed with a zero offset e.g. : CCYYMMDDHHMM+0 CCYYMMDDHH+0 Note: This may need to be taken into consideration during data migration/conversion from E2B(R2) source data.	

8. Q&As MERGED INTO THE IMPLEMENTATION GUIDE

These Q&As were incorporated into the documents included in the IG package (November 2016, Osaka).

# from ver.1.1	Date of Approval	Questions	Answers	E2B(R3) Data Element

003	**November 2014**	The lists of UCUM couldn't be found. Which website should be referred to?	Information about UCUM, including link to download the specification is available at: http://unitsofmeasure.org/trac/	
006	**November 2014**	When 'Z' was added at the end of time values as described in Appendix II I ISO 8601 Compliant XML Examples in the IG ver. 5.01, parse error occurred. Can senders use the representations of date and time such as 199411051315Z, 20090601231105.5Z, 20090601231105Z, 200906012331Z or 2009060123Z?	No, the examples described in Appendix I(C) are inappropriate. 'Z' should not be added at the end of time values. XML Schema defines the Time Zone value as <xs:pattern value="[0-9]{1,8}|([0-9]{9,14}|[0-9]{14,14}\.[0-9]+)([+|-][0-9]{1,4})?"/>, and Appendix II (B) Time Zone in the IG states that "The syntax is 'CCYYMMDDHHMMSS.UUUU[+|-ZZzz]' where digits can be omitted from right side to express less precision".	
012	**November 2014**	There are several references to M5 Identifiers in the E2B R3 Implementation Guide, please confirm these still apply?	All references to M5 Identifiers in the Implementation Guide and associated technical documents should be replaced with ISO IDMP Terms and Identifiers.	
013	**November 2014**	It is not assumed that 'In exceptional cases where the country of the primary source is not available to the sender' described in User Guidance of C.2.r.3. Is there any case that E.i.9 is used as alternative of Reporter's Country code?	No, it is not assumed that the country of the primary source is not available to sender and there is not any case that E.i.9 is used as alternative of Reporter's Country Code. In this context, the description in User Guidance of C.1.1 'in exceptional circumstances where the country of primary source is unknown, the country where the reaction occurred (E.i.9) should be used to indicate the country code' is also inappropriate. A change of E.i.9 never change Sender's (case) Safety Report Unique Identifiers.	C.1.1, C.2.r.3, E.i.9
016	**November 2014**	The Business Rule(s) of C.2.r.3 Reporter's Country Code in the IG ver. 5.01 states that "When C.2.r.5 is populated '1', nullFlavor is not allowed in this data element unless E.i.9 is populated without a nullFlavor". However nullFlavor is not allowed in E.i.9 Identification of the Country Where the Reaction / Event Occurred. Can senders use nullFlavor in C.2.r.3?	No, the description of Business Rule(s) of C.2.r.3 is inappropriate. E.i.9 only allows a two character country code.	C.2.r, E.i.9
017	**November 2014**	NullFlavor value for D.1 stated in IG ver. 5.01 doesn't match what is stated in Appendix I (B)	The business rule for ICH D.1. Patient (name or initial) concerning the use of allowable null flavor values is incomplete. Senders should refer to table in section 5.6.2 nullFlavour for Fields Required in E2B(R3) and follow	D.1

		Backwards and Forwards Compatibility Recommendations (BFC) ver. 2.00. The IG currently states that the nullFlavor value allowed is MSK and the BFC states that the nullFlavor values allowed are MSK, ASKU, NASK and UNK.	guidance concerning use of additional null flavor values for D.1., which include the use of: MSK, ASKU, NASK, UNK value options.	
018	**November 2014**	Appendix I (B) Backwards and Forwards Compatibility Recommendations (BFC) ver. 2.00 explains that "To upgrade to E2B(R3), 'Continuing (patient or parent medical history)' (i.e., B.1.7.1d or B.1.10.7.1d in E2B(R2)) is provided with value '3' (unknown) in E2B(R2), the corresponding field should be provided in E2B(R3) with the null flavour (UNK)". And the BFC also explains that "To downgrade to E2B(R2), 'Continuing (patient or parent medical history)' (i.e., D.7.1.r.3 or D.10.7.1.r.3 in E2B(R3)) has null flavor (UNK) in E2B(R3), the corresponding field in E2B(R2) should be provided with value '3' (unknown)". However, The IG currently states that the nullFlavor values allowed are MSK, ASK and NASK.	The business rule for D.7.1.r.3 or D.10.7.1.r.3 Continuing concerning the use of allowable null flavor values is incomplete. MSK, ASKU, NASK and UNK are allowed for D.7.1.r.3 and D.10.7.1.r.3. Senders should follow the guidance of upgrading to E2B(R3) or downgrading to E2B(R2) in section 5.6.3 Null Flavour for Optional Codes and Dates concerning use of the null flavour UNK for D.7.1.r.3 or D.10.7.1.r.3. This correction is reflected in the BFC version 2.01 (modified in November 2014).	D.7.1.r.3, D.10.7.1.r.3
021	**November 2014**	Test Result (code): ICH document states – "Optional, but required if F.r.2 is populated, and F.r.3.2 and F.r.3.4 is not populated". Whereas, EU implementation guide says – "Mandatory if F.r.2.2b is populated, and F.r.3.2 or F.r.3.4 is not populated.". Similar discrepancy exists for F.r.3.2 and F.r.3.4. The explicit meaning of "OR" / "AND" used in this needs to be clarified.	The conformance of F.r.3.1 is clarified as follows. Optional, but required if F.r.2 is populated, and neither F.r.3.2 nor F.r.3.4 is populated".	F.r.2, F.r.3.1, F.r.3.2, F.r.3.4
025	**November 2014**	The E2B IG implies the free text field G.k.7.r.1 is optional, however the business rules for G.k.7.r.2b. implies the use of a nullFlavor is mandatory.	The free text 'Not specified' or 'Unknown' should be expressed by using nullFlavor.	G.k.7.r.1, G.k.7.r.2b

031	**June 2016**	The conformance of D.8.r.1 Name of Drug as Reported is “Required” and the business rule states that “Nullflavor=NA” should be used when there is no previous exposure to a drug or vaccine and no other nullFlavor is allowed. Drug or vaccine exposure history may be unknown in most cases, but nullflavor=UNK is not allowed in this field. How should sender report such cases?	The conformance of D.8.r.1 in the current Implementation Guide is inappropriate. D.8.r Relevant Past Drug History can be left blank when no information is obtained. Technically, D.8.r.1 is required by the schema if any data element in section D.8.r is used. Therefore, the conformance of D.8.r.1 should be interpreted as Conditionally Required. Null flavor = UNK is allowed when no information is available but need to enter D.8.r.1.	D.8.r.

9. ANNEX: Q&As linked to the respective Sections of ICH E2B(R3) Guideline

Sections of ICH E2B(R3) Guideline	Introduction	1: Purpose	2: Background	3: Essential Components	3.4: ICH E2B(R3) DATA ELEMENTS	3.5 DOCUMENT ATTACHMENTS	4.0 THE ICSR ACKNOWLEDGEMENT TRANSACTION	APPENDICES	Other ICH Guidelines
1. Purpose									
2. Background									
3. Essential Components									
1				3.2.3.2, 3.3.6				I (A)	
2				3.3.6					
3								I(A)	
4								I (D) I (G)	
5				3.3.2					
6				3.3.6					
7									
8									
9				3.2.3					
10				3.3.7					
11				3.2.3					
12									
13				3.2.2					
4. ICH E2B(R3) DATA ELEMENTS									

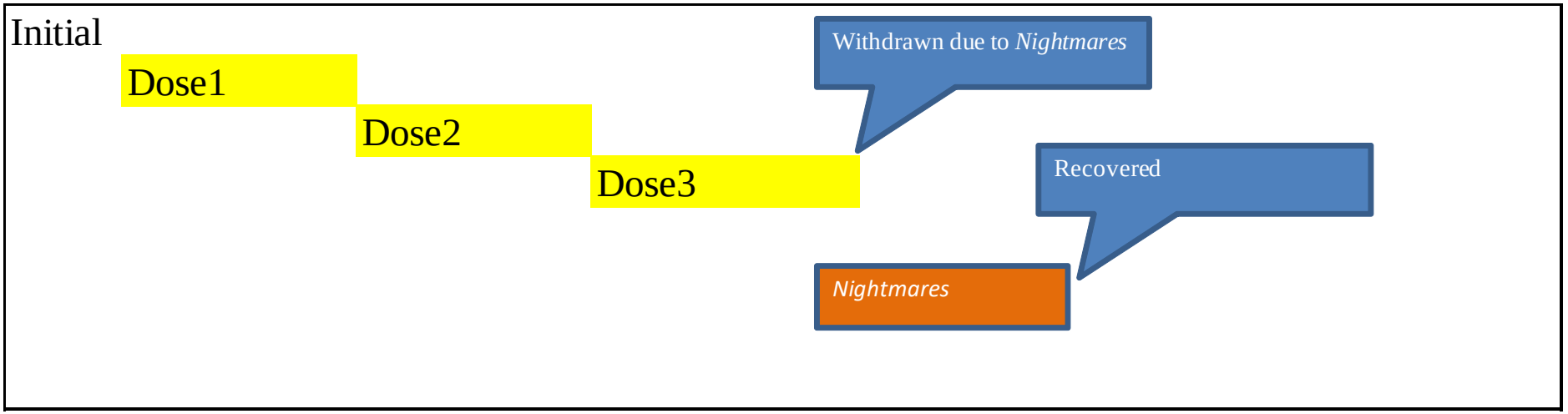
Sections of ICH E2B(R3) Guideline	Introduction	1: Purpose	2: Background	3: Essential Components	3.4: ICH E2B(R3) DATA ELEMENTS	3.5 DOCUMENT ATTACHMENTS	4.0 THE ICSR ACKNOWLEDGEMENT TRANSACTION	APPENDICES	Other ICH Guidelines
1					C.1.1, C.2.r.3, D, E.i.9				
2					C.1.3, C.2.r				
3					C.1.4, C.1.5				
4					E.i.3.2			I (G)	
5					E.i.4, E.i.5				
6					F.r.3.2				
7					F.r.3.2			I (G)	
8					F.r.3.4				
9					E.i.4, E.i.7, G.k.4.r, G.k.8, G.k.9.i.4				
10					E.i.2.1b, G.k.10.r, H.1, H.3.r				

Sections of ICH E2B(R3) Guideline	Introduction	1: Purpose	2: Background	3: Essential Components	3.4: ICH E2B(R3) DATA ELEMENTS	3.5 DOCUMENT ATTACHMENTS	4.0 THE ICSR ACKNOWLEDGEMENT TRANSACTION	APPENDICES	Other ICH Guidelines
11					C.2.r.5, C.3				
12					F.r.3.4, F.r.6				
13					G.k.6				
14					D.2.2.1, D.10				
15					D.2				
16					E.i.2.1, G.k.9.i.4				MedDRA PTC
17					G.k.2.3.r.2b				
18					D.2.2b, D.10.2.2b				
19					F.r.4, F.r.5				
20					D.6				
21					F.r.3.4				
22					D.1.1.1 – D.1.1.4				

Sections of ICH E2B(R3) Guideline	Introduction	1: Purpose	2: Background	3: Essential Components	3.4: ICH E2B(R3) DATA ELEMENTS	3.5 DOCUMENT ATTACHMENTS	4.0 THE ICSR ACKNOWLEDGEMENT TRANSACTION	APPENDICES	Other ICH Guidelines
23					D.8.r G.k.1 G.k.2 G.k.4.r G.k.4.r.8				
5. DOCUMENT ATTACHMENT									
6. THE ICSR ACKNOWLEDGEMENT TRANSACTION									
7. APPENDICES									
1								II (B)	

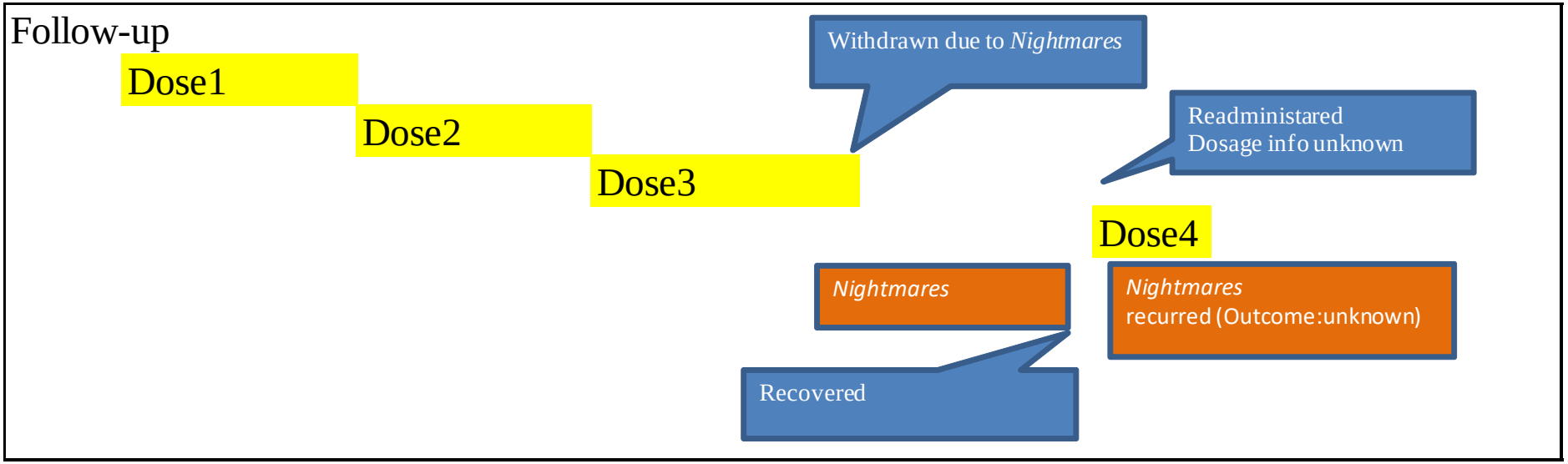
Appendix A
Example for Q&A #4.9

Consider a patient starting a drug for smoking cessation. The dose is titrated upwards over 2 weeks. After 4 weeks of use, the patient has onset of nightmares. As a result, the drug is withdrawn and subsequently the reaction/event is resolved.



Parent Element		Parent Value	Child Element		Child Value
C.1.5 Date of Most Recent Information for This Report		February 2nd			
G.k.2 Drug Identification	k=1	'QuitSmoking'			
G.k.8 Action(s) Taken with Drug	k=1	'drug withdrawn'			
			G.k.4.r Dosage and Relevant Information	k=1, r=1	January 1st: 0.5mg daily, orally, x 7 days
				k=1, r=2	January 8th: 1mg daily, orally, x 7 days
				k=1, r=3	January 15th -29th:1mg twice daily, orally (stopped)
			G.k.9.i Drug-reaction(s) / Event(s) Matrix	i=1	January 29th: onset of (E.i.1) = *Nightmares*; (E.i.7=1-Recovered/Resolved)

Follow-up ICSR:
Subsequently two weeks later, the drug re-introduced (dose, duration and action taken are unknown) and the reaction/event recurred.



Parent Element		Parent Value	Child Element		Child Value
C.1.5 Date of Most Recent Information for This Report		March 15th			
G.k.2 Drug Identification	k=1	'QuitSmoking'			
G.k.8 Action(s) Taken with Drug	k=1	'Unknown'			
			G.k.4.r Dosage and Relevant Information	k=1, r=1	January 1st: 0.5mg daily, orally, x 7 days duration
				k=1, r=2	January 8th: 1mg daily, orally, x 7 days duration
				k=1, r=3	January 15th -29th: 1mg twice daily, orally (stopped)
				k=1, r=4	February 13th: unknown, unknown
			G.k.9.i Drug-reaction(s) / Event(s) Matrix	i=1	January 29th: onset of (E.i.1) = *Nightmares*; G.k.9.i.4 = 1 yes - yes (rechallenge was done, reaction recurred); (E.i.7=0-Unknown)