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Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)

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This note for guidance replaces note for guidance EMEA/H/20665/04/Final Revision 1.

Keywords	***Business rules for Safety Message processing and Message Acknowledgment applicable to all stakeholders exchanging ICSRs electronically within the EEA.***

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Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)

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Executive summary

The purpose of this guidance is to describe the aspects of the message processing and acknowledgment generation implemented in EudraVigilance (EV). It updates and replaces the business rules and validation steps as described in the 'Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs)' (Doc. Ref. EMA/H/20665/04/Final, Revision 1).

The following aspects are outlined in detail:

- The mandatory electronic reporting essentials
- The data quality principles of ICSRs transmitted electronically
- The generation of a valid ICH Safety Message
- The requirements for the correct loading of ICH Safety Messages in EV
- The General ICH Safety Message Flow
- The ICH Safety Message Flow in EV
- The ICH Safety Message and ICSRs
- The Acknowledgement Message in EV
- The ICSR Classification in EV
- The causality assessment reporting in ICSRs from clinical trials
- The description of the mandatory ICH E2B(R2) data elements and of the complete list of validation checks performed by EV
- The concepts of the lookups for the medicinal product information validation and the rules for reporting placebos and blinded products
- The EV data security

Based on the experience gained since the first release of this guidance, new validation rules including mandatory ICH E2B(R2) data elements are being applied to all ICSRs reportable within the European Economic Area (EEA). They are applicable to all ICSRs which qualify for expedited and periodic reporting and originating within or outside the EEA. They are summarised in the table bellow. This is to achieve better adherence to the data quality principles related to ICSRs as outlined in Volume 9A of the Rules Governing Medicinal Products in the European Union (EU). Separate business rules apply for the retrospective population of the EudraVigilance Post Authorisation Module. They are described in Part III of Volume 9A.

Updates to Revision 1 of the Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Cases Safety Reports (ICSRs) are presented in blue in this document.

NEW VALIDATION RULES AND MANDATORY ICH E2B(R2) DATA ELEMENTS	
New mandatory ICH E2B(R2) data elements generating error messages	• Identification of the country of the primary source *(ICH E2B(R2) A.1.1)* • Primary source qualification *(ICH E2B(R2) A.2.1.4)* • Serious *(ICH E2B(R2) A.1.5.1)* • Seriousness criteria (for serious reports) *(ICH E2B(R2) A.1.5.2)* • Outcome of reaction/event at the time of the last observation *(ICH E2B(R2) B.2.i.8)* • Characterisation of drug role (ICH E2B(R2)B.4.k.1) • Active substance name (for reports submitted to the EudraVigilance Clinical Trial Module (EVCTM) when the drug is considered suspect or interacting) *(ICH E2B(R2) B.4.k.2.2)* • Section Relatedness of Drug to Reaction(s)/Event(s) *(ICH E2B(R2) B.4.k.18)* in relation to suspect/interacting medicinal product(s) for reports submitted to EVCTM
New ICH E2B(R2) data elements generating warning messages	• Active substance name (for reports submitted to the EudraVigilance Post-authorisation Module (EVPM) when the drug is considered suspect or interacting) *(ICH E2B(R2) B.4.k.2.2)*
New validation rules generating error messages	• Seriousness criteria should match with the ICSR Seriousness. • All reported country names, including those reported in the first part of the 'Worldwide unique case identification number', should be valid ISO3166 country codes. • For ICSRs submitted to EVPM and EVCTM ~~spontaneous reports and reports originating from non-interventional studies~~, at least one reaction should have a fatal outcome if the ICSR is serious and with the seriousness criterion 'Results in death' ~~applies~~. • Any ICSR submitted to EVPM with at least one reaction with the outcome 'fatal', should be classified as serious with a seriousness criterion 'Results in death'. This validation does not apply to EVCTM. • At least one drug in the report should be 'suspect' or 'interacting'. • All dates (including imprecise dates) should not be reported in future dates. • All start dates should be inferior or equal to their corresponding end dates. • All dates ~~except the message date and the transmission date of the ISCR~~ should be inferior or equal to the ~~date of receipt of the most recent information~~ EudraVigilance Gateway date. • No follow-up report can be submitted for cases which have been previously nullified. An error message will be generated for any additional follow-up report submitted for such cases. • For any transmission to EVCTM, 1. The 'Study name' data element should contain:

NEW VALIDATION RULES AND MANDATORY ICH E2B(R2) DATA ELEMENTS	
	1.1. For SUSARs originating in the EEA: - 'Valid EudraCT Number#Study abbreviated name', 1.2. For SUSARs originating outside the EEA: - 'Valid EudraCT Number#Study abbreviated name' or - '#Study abbreviated name' 2. For each reported event/reaction a causality assessment should be provided against any of the medicinal products reported as suspect or interacting. 3. Any initial ICSR should contain at least one reaction with a causality assessment 'Reasonable possibility' to at least one of the reported medicinal products classified as suspect or interacting. This rule is not applied to follow-up ICSRs in order to leave sponsors the possibility to downgrade the causality of an initial ICSR. • Any report from studies transmitted to EVPM, should have the data element 'Study type' populated with 'individual patient use' or 'other studies'. • The 'Test Name' data element (ICH E2B(R2) B.3.1c) should be populated with a valid MedDRA lower level term (LLT) name or code. • Only numeric MedDRA LLT codes should be used in designated fields (except in the data element 'Test Name' where valid MedDRA LLT names are also accepted). • Values of age, weight and height should not be above 150 years, 650 kg and 250 cm respectively.
New validation rules generating warning messages	• If the data element 'Pharmaceutical form (Dosage form)' is populated, the value should match with the latest version of the European Pharmacopoeia Dosage Forms list.

The new validation rules and mandatory ICH E2B(R2) data elements are applicable as outlined in the detailed Implementation Plan (Doc. Ref. EMA/665231/2008 – Revision 1).

The business rules detailed in this guidance apply to all stakeholders, which are exchanging Safety Messages and ICSRs electronically within the EEA in line with Regulation (EC) No 726/2004, Directive 2001/83/EC as amended, Directive 2001/20/EC, Volume 9A and Volume 10 of the Rules Governing Medicinal Products in the European Union.

1. Introduction (background)

This guidance describes the aspects of the Safety Message processing and Message Acknowledgment implemented in EudraVigilance (EV[1]).

It updates and replaces the business rules and validations as described in the 'Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs)' (Doc. Ref. EMA/H/20665/04/Final, Revision 1).

This guidance is applicable to all stakeholders, which are exchanging Safety Messages and ICSRs electronically within the EEA in line with Regulation (EC) No 726/2004, Directive 2001/83/EC as amended, Directive 2001/20/EC, Volume 9A and Volume 10 of the Rules Governing Medicinal Products in the European Union.

Based on the experience gained since the release of the 'Note for Guidance – EudraVigilance Human Version 7.0 – Processing of Safety Messages and Individual Case Safety Reports (ICSRs)', new validation rules and mandatory ICH E2B(R2)[2] data elements are to be applied to all ICSRs exchanged within the EEA. They are relevant to all ICSRs[3] which qualify for expedited and periodic reporting and originating within or outside the EEA. This is to achieve better adherence to the data quality principles related to ICSRs as outlined in Volume 9A of the Rules Governing Medicinal Products in the European Union.

Updates to Revision 1 of the Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Cases Safety Reports (ICSRs) are presented in blue in this document.

The new validation rules and mandatory ICH E2B(R2) data elements should be implemented as outlined in the detailed Implementation Plan (Doc. Ref. EMA/665231/2008 – Revision 1).

Separate business rules apply for the retrospective population of the EudraVigilance Post Authorisation Module. They are described in Part III of Volume 9A of the Rules Governing Medicinal Products in the European Union.

The following aspects are outlined in this document:

- The mandatory electronic reporting essentials (Chapter 2)
- The data quality principles of ICSRs transmitted electronically (Chapter 3)
- The generation of a valid ICH Safety Message (Chapter 4)
- The requirements for the correct loading of ICH Safety Messages in EV (Chapter 5)
- The General ICH Safety Message Flow (Chapter 6)
- The ICH Safety Message Flow in EV (Chapter 7)
- The Safety Messages and ICSRs (Chapter 8)
- The ICH Acknowledgement Message (Chapter 9)
- The ICSR Classification (Chapter 10)
- The causality assessment reporting in ICSRs from clinical trials (Chapter 11)

1 EudraVigilance is referred to as "EV" in the document for all aspects not depending on a particular version or release. "EVX" or "EVX.Y" stands for a specific version and release of EudraVigilance.
2 ICH Harmonised Tripartite Guideline – Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports – E2B(R2). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; Step 4 version, 5 February 2001.
3 When the transmission of Safety Reports is quoted as "ICSRs" it refers to both EVPM-ICSRs and EVCT-ICSRs.

This document also describes which aspects refer specifically to the transmission to the EudraVigilance Post-Authorisation Module (EVPM) or to the EudraVigilance Clinical Trial Module (EVCTM) and which apply to both.

- In the appendices A, B and C of this document, a detailed description of the mandatory ICH E2B(R2) data elements and of the complete list of validation checks performed by EV is provided.
- The concepts of the lookups for the medicinal product information validation and the rules for reporting placebos and blinded products are summarised in Appendix D.
- EudraVigilance data security is described in Appendix E.
- The policy on the Dosage Form Lookup List is described in Appendix F.
- The reference to the EudraVigilance User Guidance is provided in Appendix G.
- Specific local requirements are described in Appendix H.
- A table of changes is presented in Appendix I.
- The definitions of the terms in relation to the electronic exchange of safety information are available in Appendix J.

2. Mandatory Electronic Reporting Essentials

EudraVigilance is a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products in the EEA. The first operating version was launched in December 2001.

EudraVigilance supports in particular

- The electronic exchange of suspected adverse reaction reports (referred to as Individual Case Safety Reports) between the European Medicines Agency (EMA), National Competent Authorities (NCAs), marketing authorisation holders (MAHs) and Sponsors of interventional clinical trials and non-interventional studies in the EEA;
- The early detection of possible safety signals associated with medicinal products for human use;
- The continuous monitoring and evaluation of potential safety issues in relation to reported adverse reactions;
- The decision making process, based on a broader knowledge of the adverse reactions profile of medicinal products especially in the frame of the EU Risk Management Strategy.

Taking into account the pharmacovigilance activities in the pre- and post-authorisation phase, EV provides two reporting modules:

1. **The EudraVigilance Post-Authorisation Module (EVPM):** related to ICSRs which need to be reported according to Regulation (EC) No. 726/2004, Directive 2001/83/EC as amended and Volume 9A of the Rules Governing Medicinal Products in the European Union. The Safety Messages sent to this module contain spontaneous reports, reports occurring in the frame of compassionate use programmes, legacy reports and reports from non-interventional studies. The ICSRs received in this module will be referred to in this document as EVPM-ICSRs (EudraVigilance Post-authorisation Module Individual Case Safety Reports).
2. **The EudraVigilance Clinical Trial Module (EVCTM):** related to ICSRs which need to be reported in accordance with Directive 2001/20/EC and Volume 10 of the Rules Governing Medicinal Products in the European Union. The Safety Messages sent to this module contain reports from interventional clinical trials only, as defined in Article 2(a) of Directive 2001/20/EC. The ICSRs received in this module will be referred to in this document as EVCT-ICSRs (EudraVigilance Clinical Trial Individual Case Safety Reports).

3. Data Quality Principles of Individual Case Safety Reports Transmitted Electronically

Medical and administrative data related to ICSRs which qualify for expedited and periodic reporting, should be provided in line with ICH E2A, ICH E2B(R2), ICH E2D, ICH M1, ICH M2 and EU guidelines and standards. These data should be reported electronically to EV in line with Regulation (EC) No 726/2004, Directive 2001/83/EC as amended, Directive 2001/20/EC, Volume 9A and Volume 10 of the Rules Governing Medicinal Products in the European Union.

The complete information for an individual case, that is available to the sender, should be reported in each ICSR and should be entered in a fully structured format using all applicable and relevant ICH E2B(R2) data elements and terminologies, which should be repeated as necessary. This applies to all types of ICSRs, i.e. reports with initial information on the case, follow-up information and cases highlighted for nullification (ICH E2B(R2) A.1.13: 'Report nullification' set to 'yes' and ICH E2B(R2) A.1.13.1: 'Reason for nullification' completed).

Any supporting information related to the individual case should be sufficiently described within an ICSR with reference to the documents that are held by the sender (ICH E2B(R2) A.1.8.2: 'List of documents held by sender'), which may need to be provided upon request.

Any information concerning previous transmissions of the same case from other senders should be provided in the section 'Other case identifiers in previous transmissions' (ICH E2B(R2) A.1.11) where applicable. The examples described in Attachment 3 of the ICH E2B(R2) Guideline[4] should be followed. This is to aid to the detection and management of duplicates.

The detection and management of duplicated individual cases, which can occur based on the current adverse reactions reporting rules and practices, should also be addressed. Reference is made to the EU guidance on detection and management of duplicates[5].

[4] ICH Harmonised Tripartite Guideline – Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports – E2B(R2). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; Step 4 version, 5 February 2001.
[5] Draft - CHMP Guideline on Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (Doc. Ref. EMA/13432/2009), under consultation.

4. Generating a Valid ICH Safety Message

This chapter describes the process of generating a valid ICH ICSR Safety Message (also referred to as Safety Message) compliant with the ICH standards defined in the ICH M2 document[6]. This is a prerequisite for each party to successfully exchange Safety Messages with EV.

The safety message reference to the Document Type Definition (DTD) specification version 2.1 will change due to the new domain name for the European Medicines Agency. Reference should be made to the Implementation Plan dated 15 October 2010 (Doc. Ref. EMA/665231/2008 – Revision 1) as regards the date of implementation and the new safety message reference. All information in this document is presented with the new domain name, which will change from 'emea' to 'ema'.

4.1. XML

XML is the adopted standard for the exchange of Safety and Acknowledgement Messages in the European Economic Area (EEA). The eXtensible Markup Language (XML) is a subset of Standard Generalised Markup Language (SGML) that is completely compatible with SGML thereby allowing generic SGML to be served, received and processed on the web in the way that is now possible with HyperText Markup Language (HTML).

XML is used for ease of implementation and for interoperability with both SGML and HTML.

To accommodate the incorporation of multiple languages and to identify the various languages of the text within the various tags of an ICH ICSR message, a method of labelling the tags with a language attribute is used. This method is widely accepted in XML.

A valid XML Safety or Acknowledgment Message needs to include an XML header and a DTD reference. In this context, the character set used for the Safety and Acknowledgement Messages should also be declared. The accepted character sets for Safety Messages are LATIN-1 (ISO-8859-1) and UNICODE (UTF-8; UTF-16). The Acknowledgement Messages are returned by EV in UTF-16 for language compatibility.

The Safety Message should include the following XML header:

<?xml version="1.0" encoding="iso-8859-1"?> ANSI latin-1 codification 8bit per character
or
<?xml version="1.0" encoding="UTF-16"?> UNICODE UTF-16
or
<?xml version="1.0" encoding="UTF-8"?> UNICODE UTF-8

The Safety Message should include the following DTD specification version 2.1:

<!DOCTYPE ichicsr SYSTEM "http://eudravigilance.ema.europa.eu/dtd/icsr21xml.dtd">

The Acknowledgment Message should include at the message level the following XML header and DTD specification.

<?xml version="1.0" encoding="UTF-16"?>
<!DOCTYPE ichicsrack SYSTEM "http://eudravigilance.ema.europa.eu/dtd/ichicsrack11xml.dtd">

[6] ICH M2 EWG – Electronic Transmission of Individual Case Safety Report Message Specification (ICH ICSR DTD Version 2.1), Final Version 2.3, Document Revision February 1, 2001. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

There are two levels of conformance in the XML specifications: a Well-formed and a Valid message.

1. A **Well-formed** message is an XML document that conforms to the structural rules of XML:
    - The first line should be the XML document declaration as specified above
    - The document should contain at least one element (or tag)
    - Every starting tag should have a closing tag
    - <tag/> is also permitted for tags that do not contain data
    - Tags cannot overlap.

In order to improve the readability of the XML file, a carriage return should be inserted after each closing tag e.g. <start tag>Value</end tag> [CR][LF]. CR: carriage return, LF: line feed.

In addition, as XML is case sensitive, all the fields and attributes names have to be in lower case in order to comply with the XML DTD.

2. A **Valid XML** file is one, which has a DTD reference and which is conformed to the DTD.

The DTD is a document that defines the valid elements (tags) and attributes that may appear in a particular type of XML document. It also defines element nesting rules for the document. A valid XML file should also be well-formed.

The following XML special characters (excluding quotation marks) ">", "<" and "&" when occurring in text should always be replaced by ">" "<" and "&" respectively.

Regarding all aspects of XML, the W3C standards should be followed as published at http://www.w3.org/

5. Requirements for the Correct Loading of ICH Safety Messages in EudraVigilance

This chapter defines the rules that should be followed to be able to successfully exchange Safety Messages with EV. Appendixes A to C describe these rules in detail.

For a Safety Message to be successfully loaded in EV, it should conform to the Safety Message standards (ICH DTD) and should respect the business rules defined in Appendixes A to C.

6. The General ICH Safety Message Flow

This chapter describes the Safety Message exchange with EV between all relevant parties involved in safety monitoring in the EEA. In order to transmit a Safety Message to the correct receiver it is required to correctly specify the data element *messagesenderidentifier* (ICH M2 M.1.5) and the data element *messagereceiveridentifier* (ICH M2 M.1.6).

The data element *messagesenderidentifier* (ICH M2 M.1.5) should be the sender's own organisation identifier (organisation ID) and should be reported also in the data element *senderorganization* (ICH E2B(R2) A.3.1.2) in each ICSR attached to the Safety Message.

Both data elements *messagesenderidentifier* (ICH M2 M.1.5) and *messagereceiveridentifier* (ICH M2 M.1.6) should correspond to the organisation identifier list maintained by EMA, i.e. only those parties that are registered with EMA are able to exchange Safety Messages either with EMA (EV) or other registered parties (EudraVigilance community).

The list of all possible parties refers to NCAs, MAHs, Applicants for a Marketing Authorisation and Sponsors of interventional clinical trials and non-interventional studies (hereafter referred to as Applicants and Sponsors respectively).

There are two possible ways of exchanging Safety Messages between registered pharmacovigilance parties in the EEA.

1. Using an **ESTRI Gateway**: A tool providing a fully automated way to exchange Safety and Acknowledgment Messages between the locally established pharmacovigilance system of a party in the EEA (e.g. a NCA) and another party (e.g. a MAH) of the EudraVigilance community;
2. Using the **EudraVigilance WEB Trader**: A web tool that is made available by EMA to interested registered parties, providing a way to exchange Safety and Acknowledgment Messages in a semi-automatic way using the EudraVigilance web application, EVWEB.

Inside the EudraVigilance community, the following communication scenarios are possible:

Reporting to EudraVigilance (EVPM and EVCTM):

- NCAs, MAHs, Applicants and Sponsors send Safety Messages to EMA. They can submit ICSRs to EVPM and to EVCTM;
- EMA sends Acknowledgments Messages to NCAs, MAHs, Applicants and Sponsors.

Re-routing via EudraVigilance:

- MAHs, Applicants and Sponsors send Safety and Acknowledgment Messages to NCAs in the EEA;
- NCAs send Safety and Acknowledgments Messages to MAHs, Applicants and Sponsors.

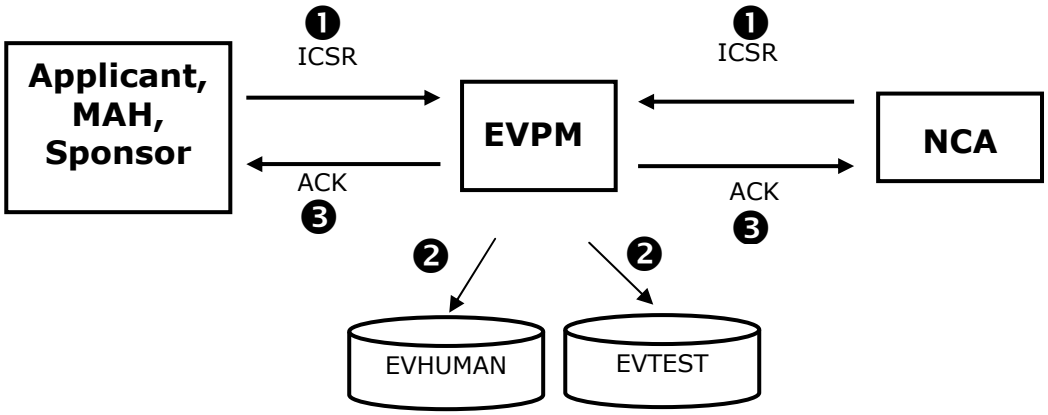
6.1. Reporting to EVPM (Figure 1):

The example in Figure 1 reflects the exchange of a Safety Message including one or several ICSRs from a MAH, Applicant or Sponsor to EV and from a NCA to EV.

1. A NCA, MAH, Applicant or Sponsor sends ICSR(s) in a Safety Message to EV;
2. The Safety Message is delivered to the EV compliance testing environment or the EV production environment of EVPM if the receiver identifier specified in the Safety Message is EVTEST or EVHUMAN respectively;

3. EV sends an Acknowledgement Message (ACK) to confirm the receipt of the Safety Message and of the ICSR(s).

Figure 1. Exchange of a Safety Message in EVPM

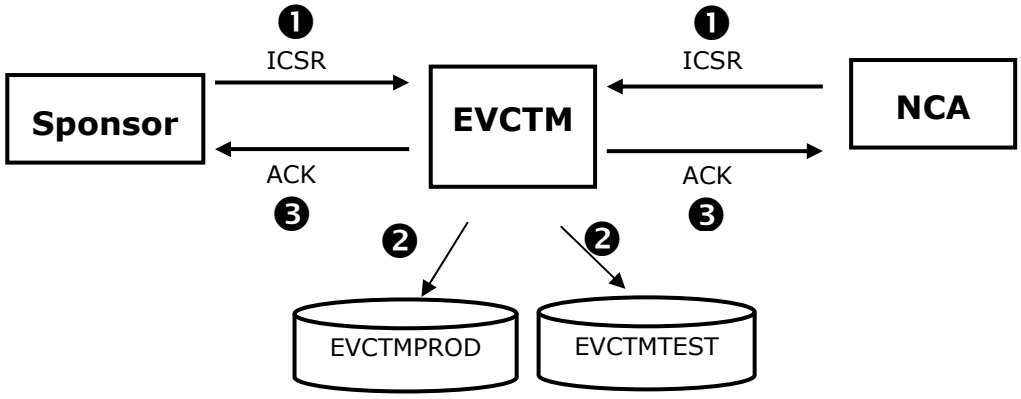


6.2. Reporting to EVCTM (Figure 2):

The example in Figure 2 reflects the exchange of a Safety Message including one or several ICSRs from a Sponsor of an interventional clinical trial to EV and from a NCA to EV.

1. A NCA or Sponsor of an interventional clinical trial sends ICSR(s) in a Safety Message to EV;
2. The Safety Message is delivered to the EV compliance testing environment or to the EV production environment of EVCTM if the receiver identifier specified in the Safety Message is EVCTMTEST or EVCTMPROD respectively;
3. EV sends an Acknowledgement Message (ACK) to confirm the receipt of the Safety Message and of the ICSR(s).

Figure 2. Exchange of a Safety Message in EVCTM



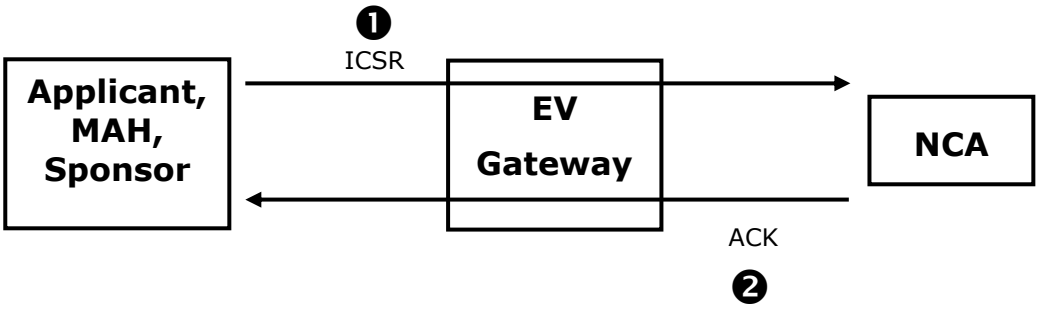
6.3. Re-routing via EV:

A MAH, Applicant or Sponsor sends a Safety Message to a NCA in the EEA:

The example in Figure 3 reflects the exchange of a Safety Message including one or several ICSRs from a MAH, Applicant or Sponsor to a NCA via EV.

1. A MAH, Applicant or Sponsor sends ICSR(s) included in a Safety Message via EV to a NCA;
2. A NCA sends an Acknowledgement Message (ACK) via EV to confirm the receipt of the Safety Message and of the ICSR(s).

Figure 3. Submission of Safety Message by MAH, Applicant or Sponsor to NCA via EV

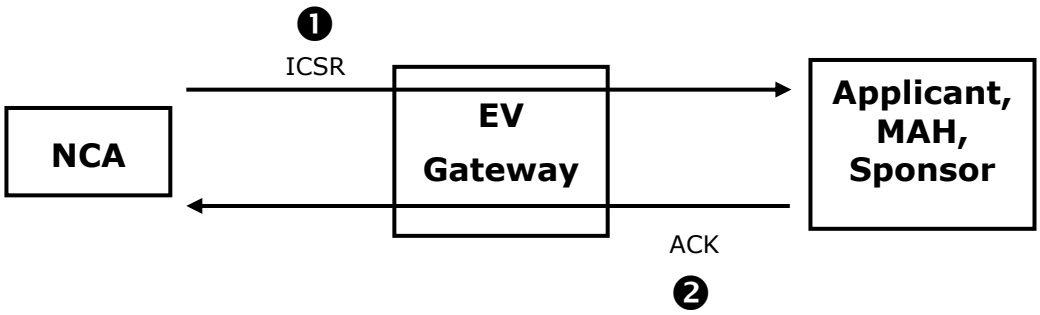


A NCA in the EEA sends a Safety Messages to a MAH, Applicant or Sponsor:

The example in Figure 4 reflects the exchange of a Safety Message including one or several ICSRs from a NCA to a MAH, Applicant or Sponsor via EV.

1. A NCA sends ICSR(s) in a Safety Message via EV to a MAH, Applicant or Sponsor;
2. The MAH, Applicant or Sponsor sends an Acknowledgement Message (ACK) via EV to confirm the receipt of the Safety Message and of the ICSR(s).

Figure 4. Submission of Safety Message by NCA to MAH, Applicant or Sponsor via EV



7. The ICH Safety Message Flow in EudraVigilance

This chapter describes the Safety Message flow in EV and outlines when an Acknowledgment Message is generated and when it is not generated (Figure 5). The latter may be the case, if for example, the Safety Message is not well-formed and/or not valid (refer to Chapter 4 for generating a valid Safety Message).

EV performs a validation of any incoming Safety Message in two steps:

7.1. Inbound Parsing Validation

EV performs a basic validation of any incoming Safety Message against the specified DTD. The sender is responsible for including the correct Safety Message XML header as specified in Chapter 4. In case the sender has not included the correct DTD reference header as indicated in Chapter 4, the return of an Acknowledgment Message cannot be guaranteed by the receiver.

In case of the detection of a parsing error by EV, the following scenarios may occur:

- If during the parsing process of the Safety Message, EV can detect a valid sender identifier, an Acknowledgement Message will be created and sent to the sender, listing the detected error. The *transmissionacknowledgementcode* reported in the data element (ICH M2 A.1.6) will be '03' i.e. no data extracted.
- If during the parsing process of the Safety Message, EV cannot detect a valid sender identifier, an Acknowledgement Message cannot be created, as the sender cannot be identified. In this case no Acknowledgement Message will be returned.
- If the parsing process of the Safety Message is successful, but EV cannot recognize the receiver identifier because the receiver is not registered with EMA, an Acknowledgement Message will be created indicating the error. The *transmissionacknowledgementcode* reported in the data element (ICH M2 A.1.6) will be '03' i.e. no data extracted.

If the Safety Message is valid according the Safety Message DTD validation, EV can perform one of the following actions:

- Re-route the Safety Message to the partner specified in the data element *messagereceiveridentifier* (ICH M2 M.1.6). The partner should be a registered organisation in the EudraVigilance community otherwise EV will return a Transmission Acknowledgement Code '03' i.e. no data extracted;
- Upload the Safety Message with the Inbound Load Process into EV.

7.2. Inbound Loading Process into EV

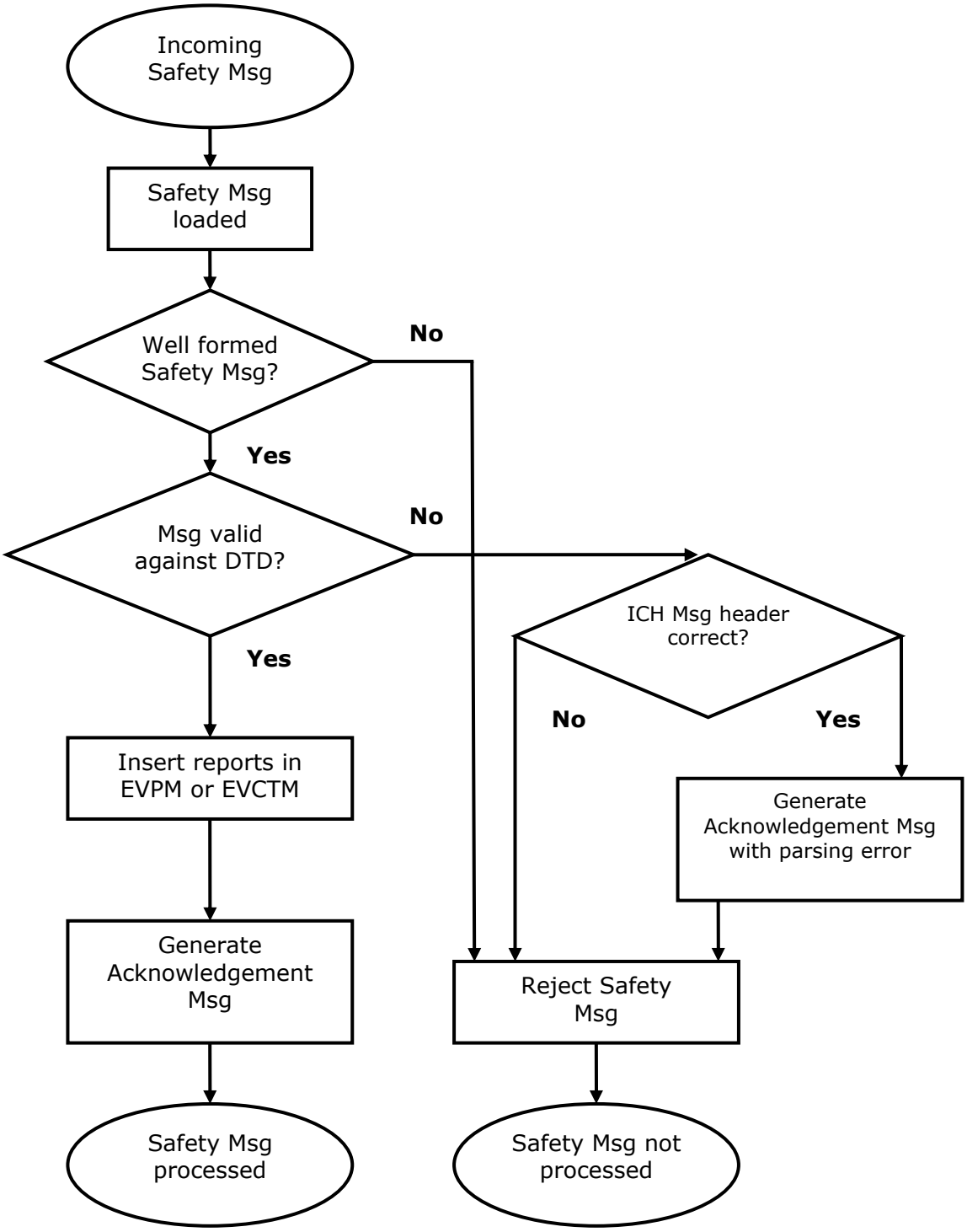
The processing of the Safety Messages refers only to the XML documents addressed to one of the receiver identifiers of the EudraVigilance System (EVTEST, EVHUMAN, EVCTMTEST, EVCTMPROD).

If the Safety Message is valid according to the XML structural rules and the DTD reference, the message will be delivered to one of the following modules in order to be processed and uploaded:

- The test environment of EVPM if the value in the data element *messagereceiveridentifier* (ICH M2 M.1.6) is EVTEST.
- The test environment of EVCTM if the value in the data element *messagereceiveridentifier* (ICH M2 M.1.6) is EVCTMTEST.

- The production environment of EVPM if the value in the data element *messagereceiveridentifier* (ICH M2 M.1.6) is EVHUMAN.
- The production environment of EVCTM if the value in the data element *messagereceiveridentifier* (ICH M2 M.1.6) is EVCTMPROD.

Figure 5. Safety Message (MSg) flow



8. ICH Safety Messages and Individual Case Safety Reports (ICSRs)

This chapter describes the structures of Safety Messages and ICSRs.

A Safety Message can be regarded as an envelope, which may contain one or more ICSRs. Every message contains a Message Header part which should include information on the sender, the receiver, the message date and a unique message identification number. For further details about the message rules and specifications, please refer to the official ICH documentation as referred to in Chapter 4. The accepted values for the elements of the Message Header and ICSRs are detailed in the Appendixes A to C.

8.1. Message Header

The Safety Message Header is the basis for the establishment of an Electronic Data Interchange (EDI) trading partnership between two parties. It contains the following elements:

8.1.1. Message Type

The data element *messagetype* (ICH M2 M.1.1) contains information on the type of information being transmitted. It is specified in the ESTRI recommendation 5.3[7].

8.1.2. Message Format Version

The data element *messageformatversion* (ICH M2 M.1.2) contains the version number of the DTD. It is specified in the ESTRI recommendation 5.3.

8.1.3. Message Format Release

The data element *messageformatrelease* (ICH M2 M.1.3) specifies the release number of the message format version of the DTD. It is specified in the ESTRI recommendation 5.3.

8.1.4. Message Number, Sender defined message number (unique to the sender)

The data element *messagenumb* (ICH M2 M.1.4) is a unique tracking number assigned to a specific Safety Message file transmitted by the sender. This message number is unique to the sender.

8.1.5. Message Sender Identifier

The data element *messagesenderidentifier* (ICH M2 M.1.5) identifies the sender of the Safety Message i.e. the organisation identifier chosen by the sender in the registration process with EMA.

8.1.6. Message Receiver Identifier

The data element *messagereceiveridentifier* (ICH M2 M.1.6) identifies the intended recipient of the transmission of the Safety Message i.e. the organisation identifier, chosen by the recipient during the registration process with EMA.

[7] ICH M2 – Electronic Standards for the Transfer of Regulatory Information (ESTRI) – Recommendation Notebook Version 3.0. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

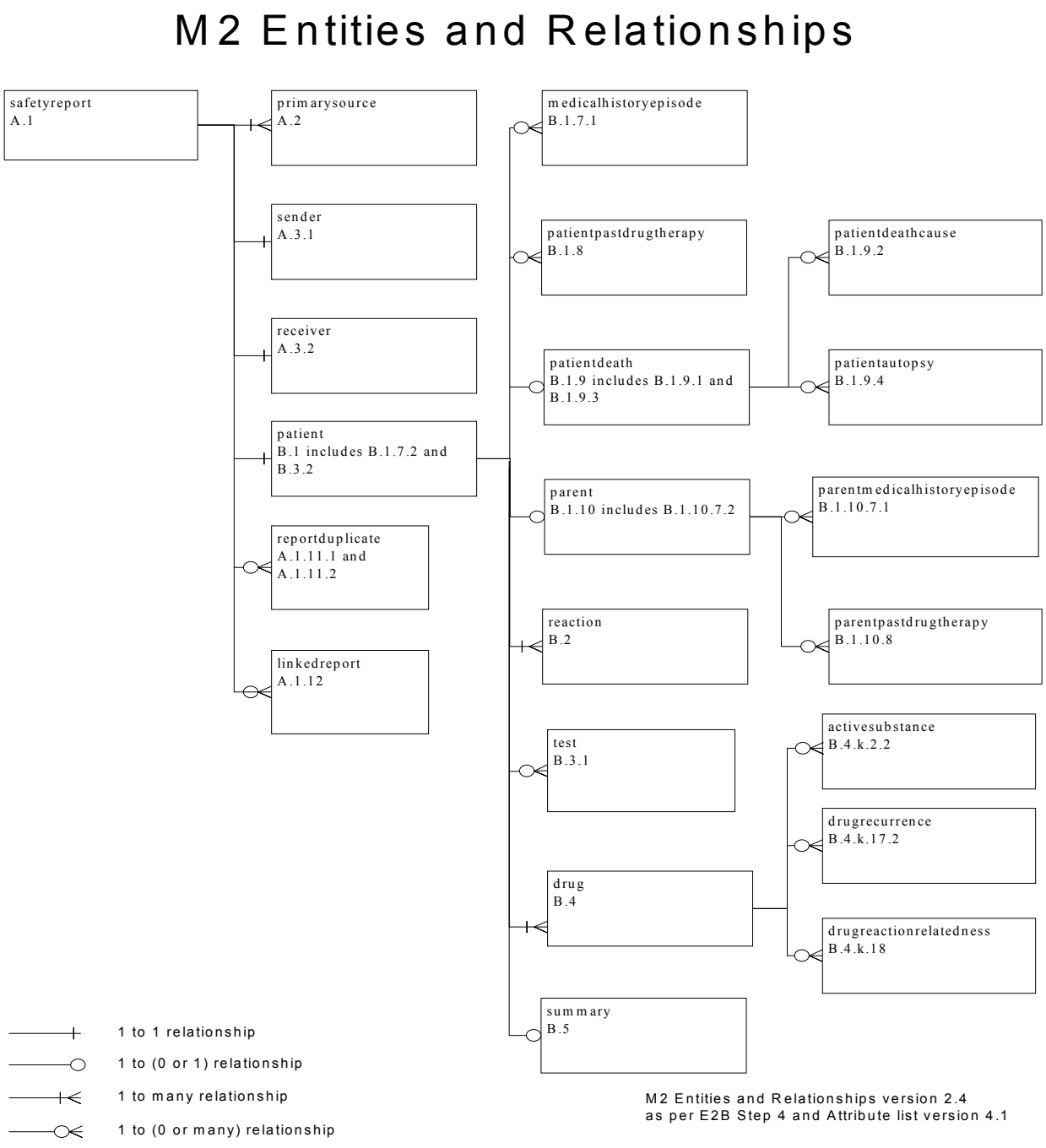
8.1.7. Message Date

The data element messagedate (ICH M2 M.1.7b) provides information regarding the date on which the Safety Message was initiated.

8.2. Individual Case Safety Report (ICSR)

The entities of an ICSR in EV are organised following a hierarchical (parent-child) structure as shown in Figure 6 (Source: ICH M2 document).

Figure 6. M2 Entities and Relationships



9. The ICH Acknowledgment Message

This chapter describes the structures and the fields values of an Acknowledgment Message created and returned by EV to the sender. It provides the sender with

- The results of the outcome of the loading process and any errors and warnings detected by the parsing process,
- The updated classification status.

The Acknowledgment structure follows the ICH-ICSR specifications detailed in the ICH M2 EWG document [8].

9.1. Acknowledgment Message Elements

An Acknowledgment Message created and returned to the sender contains the elements presented in Table 1 and described in the ICH M2 EWG and ICH E2B(R2)[9] documents.

Table 1. Acknowledgment Messages elements

DATA ELEMENT	DTD DESCRIPTOR	FIELD LENGTH	FIELD VALUES	MANDATORY
M.1	**Ichicsrmessageheader**			
M.1.1	Messagetype	16AN	ichicsrack	Yes
M.1.2	Messageformatversion	3AN	1.1	Yes
M.1.3	Messageformatrelease	3AN	1.0	Yes
M.1.4	Messagenumb	100AN		Yes
M.1.5	Messagesenderidentifier	60AN		Yes
M.1.6	Messagereceiveridentifier	60AN		Yes
M.1.7a	messagedateformat	3N	204	Yes
M.1.7b	Messagedate	14N		Yes
A.1	**Messageacknowledgment**			
A.1.1	icsrmessagenumb	100AN		Yes
A.1.2	localmessagenumb	100AN	Locally Assigned	
A.1.3	Icsrmessagesenderidentifier	60AN		Yes
A.1.4	Icsrmessagereceiveridentifier	60AN		Yes
A.1.5a	Icsrmessagedateformat	3N	204	Yes
A.1.5b	Icsrmessagedate	14N		Yes
A.1.6	transmissionacknowledgmentcode	2N	01= All Reports loaded into database 02 = ICSR Error, not all reports loaded into the database, check section B 03 = XML parsing error, no data extracted	Yes
A.1.7	Parsingerrormessage	250 AN		Yes if A.1.6 value is (03)
B.1.	**Reportacknowledgment**			
B.1.1	Safetyreportid	100AN		Yes
B.1.2	safetyreportversion	2AN		
B.1.3	Localreportnumber	100AN		
B.1.4	Authoritynumber	100AN		Yes
B.1.5	companynumber	100AN		One of B.1.4 or B.1.5
B.1.7a	Receiptdateformat	3N	102	
B.1.7b	Receiptdate	8N		

[8] ICH M2 EWG – Electronic Transmission of Individual Case Safety Report Message Specification (ICH ICSR DTD Version 2.1), Final Version 2.3, Document Revision February 1, 2001. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

[9] ICH Harmonised Tripartite Guideline – Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports – E2B(R2). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; Step 4 version, 5 February 2001.

DATA ELEMENT	DTD DESCRIPTOR	FIELD LENGTH	FIELD VALUES	MANDATORY
B.1.8	Reportacknowledgmentcode	2N	01=Report Loaded Successfully 02=Report Not Loaded	Yes
B.1.9	Errormessagecomment	250AN		

Table Legend:

Data Element: Element (or section) standard code

DTD Descriptor: Element (or section) standard name

Field Length: Maximum number of characters for an element ('N': numeric values accepted, 'AN': alphanumeric values accepted)

Field Values: List of admissible values (if it exists)

Data Format Codes: 102 = CCYYMMDD *(example: 12 JANUARY 1997 --> 19970112)*

204 = CCYYMMDDHHMMSS (example: 12 JANUARY 1997 14:02:17 --> 19970112140217)

Mandatory: Indicates that Element (or section) is mandatory (if nothing is specified, it is considered optional)

9.2. Acknowledgment Message elements descriptions

The elements descriptions and the EV assigned values are the following:

9.2.1. M.1 ICSR Message Header

This is the standard ICH M2 message header, similar to the message header in the ICH ICSR DTD. This section specifies the message type, such as ICSR Acknowledgments, version, and release number of the DTD. This message header section assumes the establishment of an EDI trading partnership agreement that will help drive the designation of the message identification number, sender ID, receiver ID, message date, and the acknowledgment for the submission of the XML file containing multiple ICSRs.

M.1.1 Message type

The data element *messagetype* (ICH M2 M.1.1) contains information on the type of information being transmitted.

- Default EV value is *'ichicsrack'*

M.1.2 Message Format Version

The data element *messageformatversion* (ICH M2 M.1.2) contains the version number of the DTD. The value of the version number can be obtained from the ICSR Acknowledgment Message DTD.

- Default EV value is '1.1'

M.1.3 Message Format Release

The data element *messageformatrelease* (ICH M2 M.1.3) contains the release number of the message format version number of the DTD. The value of the release number can be obtained from the documentation section of the ICSR Acknowledgment Message DTD.

- Default EV value is '1.0'

M.1.4 Message Number, sender defined message number (unique to the sender)

The data element *messagenumb* (ICH M2 M.1.4) is a unique tracking number assigned to a specific Acknowledgment Message file by the sender of the Acknowledgment. This message number is unique to the sender.

- EV value is 'EU-EC-M-xxx-ACK' where xxx is the last numerical part of the data element *localmessagenumb* (ICH M2 A.1.2)

M.1.5 Message Sender Identifier

The data element *messagesenderidentifier* (ICH M2 M.1.5) defines the sender of the Acknowledgment.

- The sender ID generated by EV for an Acknowledgment Message is one of the following, depending to which module the original Safety Message was addressed:
  - 'EVTEST' (Test environment – EVPM)
  - 'EVHUMAN' (Production environment – EVPM)
  - 'EVCTMTEST' (Test environment – EVCTM)
  - 'EVCTMPROD' (Production environment – EVCTM)
- The value generated by EV for an Acknowledgment Message is identical to the value in the data element *receiverorganization* (ICH E2B(R2) A.3.2.2a) of the ICSR

M.1.6 Message Receiver Identifier

The data element *messagereceiveridentifier* (ICH M2 M.1.6) defines the receiver of the Acknowledgment.

- The value generated by EV for an Acknowledgment Message is identical to the value in the data element *senderorganization* (ICH E2B(R2) A.3.1.2) of the ICSR

M.1.7a and b Message Date and Format

The data element *messagedate* (ICH M2 M.1.7b) is the date when the Acknowledgment Message is initiated.

- The default EV value for the data element *messagedateformat* (ICH M2 M.1.7a) is '204' i.e. CCYYMMDDHHMMSS

9.2.2. A.1 Message Acknowledgment

This is a section header that specifies the Safety Message that is being acknowledged. This section also assumes the establishment of an EDI trading partnership agreement that will help drive the designation of the message identification number, local message number, sender ID, receiver ID, message date, and the Acknowledgment for the submission of the XML file containing multiple ICSRs.

A.1.1 ICSR Message Number

The value in the data element *icsrmessagenumb* (ICH M2 A.1.1) is a unique tracking number assigned to a specific Safety Message file by the sender of the Safety Message. This ICSR message number is unique to the sender of the Safety Message.

- EV value is the same as for the data element *messagenumb* (ICH M2 M.1.4) of the incoming Safety Message

A.1.2 Local Message Number

The value in the data element *localmessagenumb* (ICH M2 A.1.2) is assigned to the Safety Message by the receiving organisation. The length, data type, and value are determined by the receiving organisation.

- EV local message number matches part of the value in data element ICH M2 M.1.4 ('EU-EC-M-xxx-ACK')

A.1.3 ICSR Message Sender Identifier

The data element *icsrmessagesenderidentifier* (ICH M2 A.1.3) defines the sender of the ICSRs which are being acknowledged, i.e., the value of the data element *senderorganization* (ICH E2B(R2) A.3.1.2) relating to the sender of the ICSRs.

- The value generated by EV is the same as for the data element *messagesenderidentifier* (ICH M2 M.1.5) of the incoming Safety Message

A.1.4 ICSR Message Receiver Identifier

The data element *icsrmessagereceiveridentifier* (ICH M2 A.1.4) defines the receiver of the ICSR reports, i.e. the value of the data element *receiverorganization* (ICH E2B(R2) A.3.2.2a) relating to the receiver identifier of the ICSRs.

- The value generated by EV is one of the following, depending to which module the original Safety Message was addressed:
  - 'EVTEST' (Test environment – EVPM)
  - 'EVHUMAN' (Production environment – EVPM)
  - 'EVCTMTEST' (Test environment – EVCTM)
  - 'EVCTMPROD' (Production environment – EVCTM)
- The value generated by EV is the same as the one reported in the data element *messagereceiveridentifier* (ICH M2 M.1.6) of the incoming Safety Message.

A.1.5a and b ICSR Message Date and Format

The data element i*csrmessagedate* (ICH M2 A.1.5b) is the date when the Safety Message was initiated.

- EV reports the same value as specified in the data element *messagedate* (ICH M2 M.1.7b) in the original incoming Safety Message
- The default EV value for the data element *icsrmessagedateformat* (ICH M2 A.1.5a) is '204' i.e. CCYYMMDDHHMMSS

A.1.6 Transmission Acknowledgment Code

The data element *transmissionacknowledgmentcode* (ICH M2 A.1.6) is a 2N field that informs the sender of the ICH ICSR message to either re-send the complete transmission or await Acknowledgment on individual reports.

- EV possible Transmission Acknowledgment Code values are:
  - 01 = All Reports loaded into database
  - 02 = ICSR Error, not all reports loaded into the database
  - 03 = XML parsing error, no data extracted

A.1.7 Parsing Error Message (See Chapter 9.3 for more details)

The data element *parsingerrormessage* (ICH M2 A.1.7) is a text field (250 characters) which is used to briefly describe the types of XML errors detected while parsing the file. This field is used when the value of the data element *transmissionacknowledgementcode* (ICH M2 A.1.6) is '03'.

- EV reports potential parsing errors generated by the system's internal XML parser

9.2.3. B.1. Report Acknowledgment

This section header provides an acknowledgment for each ICSR included in the Safety Message file. It is a repeatable section for each ICSR that has to be acknowledged. In order to inform the sender about the outcome of the ICSR classification in EV and the possible warnings encountered as result of the validation process, this section is always included in the Acknowledgment Message.

B.1.1 Safety Report ID

The Safety Report identifier data element contains the value assigned by the sender to identify each ICSR.

- The data element *safetyreportid* (ICH M2 B.1.1) in the Report Acknowledgment is the same value as for the data element *safetyreportid* (ICH E2B(R2) A.1.0.1) of the ICSR

B.1.2 Safety Report Version Number

The Safety Report version is a number assigned by the sender of the ICSR to differentiate the versions of an ICSR.

- EV value is the same as specified in the ICH M2 data element *safetyreportversion* of the corresponding ICSR

B.1.3 Local Report Number

The local report number is a value assigned to each ICSR by the receiving organisation of the Safety Message.

- EV reports the system's internal unique number

B.1.4 Regulatory Authority's Case Report Number

The value in the data element *authoritynumber* (ICH M2 B.1.4) is a unique identifier that is equivalent to the national regulatory authority's case report number.

- EV value is the same as specified in the data element *authoritynumb* (ICH E2B(R2) A.1.10.1) of the corresponding ICSR

B.1.5 Other Sender's Case Report Number

The value in the data element *companynumber* (ICH M2 B.1.5) is a unique identifier assigned by a sender. Senders should ensure a single international number to facilitate the unique identification of an ICSR that may have been sent to several receivers and subject to multiple re-transmissions.

- EV value is the same as the value assigned in the data element *companynumb* (ICH E2B(R2) A.1.10.2) of the corresponding ICSR

B.1.7a and b Date of Receipt of the Most Recent Information and Format

The data element *receiptdate* (ICH M2 B.1.7b) should be used to record the date of the most recent information of the case.

- EV value is the same as the value assigned in the data element *receiptdate* (ICH E2B(R2) A.1.7b) of the corresponding ICSR
- The default EV value for the data element *receiptdateformat* (ICH M2 B.1.7a) is '102' i.e. CCYYMMDD

B.1.8 Acknowledgment Code for a Report

This field is used to indicate if an ICSR was successfully loaded into the application database or if it failed the loading process. If there is an error, the application may indicate the nature of the error in the data element *errormessagecomment* (ICH M2 B.1.9). The data element *reportacknowledgmentcode* (ICH M2 B.1.8) is a 2N field.

- EV possible Acknowledgment Code values for an ICSR are:
  - 01 = Report Loaded Successfully
  - 02 = Report Not Loaded

B.1.9 Error Message or Comment (See Chapters 9.4 and 9.5 for more details)

The data element *errormessagecomment* (ICH M2 B.1.9) is a text field (250 characters) and it is populated by EV with the error and warnings information, if applicable, encountered during the validation process of the ICSR.

In order to make the sender aware of the classification results and of the possible warnings detected in the validation processes of the ICSR, EV always adds the data element *errormessagecomment* (ICH M2 B.1.9) in the Report Acknowledgment section of every Acknowledgment Message.

9.3. Parsingerrormessage

The *parsingerrormessage* data element (ICH M2 A.1.7) is a text field (250 characters) and it is included in the Acknowledgment Message only if the data element *transmissionacknowledgmentcode* (ICH M2 A.1.6) value is '03' i.e. XML parsing error, no data extracted. This field describes the error generated by the EV XML parser.

9.3.1. Parsingerrormessage example

The following section extracted from a Safety Message includes the element <xyz>, which is not included in the DTD specification. An example for an Acknowledgment Message is included specifying the error detected by EV during the validation processes.

Message:

```
……
<?xml version="1.0" encoding="iso-8859-1"?>
<!DOCTYPE ichicsr SYSTEM "http://eudravigilance.ema.europa.eu/dtd/icsr21xml.dtd">
<ichicsr lang="en">
<ichicsrmessageheader>
<messagetype>ichicsr</messagetype>
<messageformatversion>2.1</messageformatversion>
<messageformatrelease>1.0</messageformatrelease>
<messagenumb>DP111</messagenumb>
<messagesenderidentifier>ACME</messagesenderidentifier>
<messagereceiveridentifier>EVTEST</messagereceiveridentifier>
<messagedateformat>204</messagedateformat>
<messagedate>20020422040447</messagedate>
/ichicsrmessageheader>
<safetyreport>
<xyz>1</xyz>
<safetyreportid>FR-ACME-DP2002042204</safetyreportid>
……
```

Acknowledgment:

```
……
<icsrmessagedate/>
<transmissionacknowledgmentcode>03</transmissionacknowledgmentcode>
<parsingerrormessage> Reason: Element content is invalid according to the
DTD/Schema.Expecting: safetyreportversion, safetyreportid </parsingerrormessage>
</messageacknowledgment>
……
```

9.4. Errormessagecomment

The data element *errormessagecomment* (ICH M2 B.1.9) appears in the section *reportacknowledgment* (ICH M2 B.1), which is provided for each ICSR included in the Safety Message.

According to ICH specification, the *reportacknowledgment* section should be added to the Acknowledgment Message only if the value for the data element *reportacknowledgmentcode* (ICH M2 B.1.8) is '02' i.e. report not loaded. However in order to make the sender aware of the report classification outcome, EV systematically includes this field for each ICSR.

- If the value for the data element *reportacknowledgmentcode* (ICH M2 B.1.8) is '02' there are one or more errors in the ICSR and no data have been loaded successfully. In the data element *errormessagecomment* (ICH M2 B.1.9), EV describes the errors and warnings encountered during the validation processes of the ICSR. Then EV adds the classification outcome for the analysed ICSR(s)
- If the value for the data element *reportacknowledgmentcode* (ICH M2 B.1.8) is '01' the corresponding ICSR is loaded successfully and in the data element *errormessagecomment* (ICH M2 B.1.9) the classification result is presented. In case the validation processes of the ICSR have

detected warnings, their textual description is included in the data element *errormessagecomment* (ICH M2 B.1.9)

9.4.1. Errormessagecomment example (correct)

If an ICSR is completely correct, without warnings, the following example shows the *errormessagecomment* as created by EV:

Acknowledgment:

```
……
<reportacknowledgmentcode>01</reportacknowledgmentcode>
<errormessagecomment>safety report loadedComments: Parsing process: Correct Report
Classification: new: EU-EC-3191 = Replaced Report - old: EU-EC-3174 = Case report</
errormessagecomment>
……
```

9.4.2. Errormessagecomment example - Error

The following example shows a possible Report Acknowledgment for an ICSR containing an error (the value 999 in the data element *transmissiondateformat* (ICH E2B(R2) A.1.3a) is not accepted).

Message:

```
……
<safetyreport>
<safetyreportversion>1</safetyreportversion>
<safetyreportid>FR-ACME-DP2002042204</safetyreportid>
<primarysourcecountry>FR</primarysourcecountry>
<occurcountry>FR</occurcountry>
<transmissiondateformat>999</transmissiondateformat>
<transmissiondate>20020422</transmissiondate>
……
```

Acknowledgment:

```
……
<reportacknowledgmentcode>02</reportacknowledgmentcode>
<errormessagecomment>safety report not loaded; Validated against <current business rules>;
Comments: 1- In section SAFETYREPORT on field transmissiondateformat (ICH E2B(R2) A.1.3a)
value: 999 reported Error SCHEMA - Enumeration constraint failed. The element:
'transmissiondateformat' has an invalid value according to its data type.; Parsing process:
Report with Errors </errormessagecomment>
……
```

9.4.3. Errormessagecomment example - warning

The following example shows the possible Report Acknowledgment for an ICSR loaded with warnings. In this case the medicinal product PRODUCTEXAMPLE is not included in the EudraVigilance Medicinal Product Dictionary.

If the Report Acknowledgment contains warnings the corresponding ICSR is loaded successfully in the system and the value for the data element *reportacknowledgmentcode* (ICH M2 B.1.8) is '01' i.e. report loaded successfully.

Message:

```
……
```

<drug>
<drugcharacterization>1</drugcharacterization>
<medicinalproduct>PRODUCTEXAMPLE</medicinalproduct>
<drugauthorizationnumb>22222</drugauthorizationnumb>
……

Acknowledgment:

……
<reportacknowledgmentcode>01</reportacknowledgmentcode>
<errormessagecomment>safety report loaded; Validated against <current business rules>;
Comments: 1- In section DRUG on field medicinalproduct (*ICH E2B(R2) B.4.k.2.1*) value:
PRODUCTEXAMPLE reported Warning BUSINESSRULES - LOOKUP - CheckSub
PRODUCTEXAMPLE must be a valid Medicinal Product; Parsing process: Report with Warnings;
Classification: new: EU-EC-M-3202 = Case Report - old: EU-EC-M-3174 = Replaced Report
</errormessagecomment></reportacknowledgment>
……

9.5. Errormessagecomment Structure

Example of *Errormessagecomment* elements structure for the Acknowledgement example described in Chapter 9.4.3:

❶ Safety report loaded; Validated against <current business rules>

❷ Comments:

❸ 1- In section DRUG on field medicinalproduct (ICH E2B(R2) B.4.k.2.1) value:
PRODUCTEXAMPLE reported Warning BUSINESSRULES - LOOKUP - CheckSub
PRODUCTEXAMPLE must be a valid Medicinal Product;

❹ Parsing process: Report with Warnings;

❺ Classification:

❻ new: EU-EC -3202 = Case Report –

❼ old: EU-EC -3174 = Replaced Report

Each section of the error message contains:

❶ **Loading & Validation Information:**

- Safety report loaded
- Safety report not loaded
- Validated against <current business rules>

❷ **Error and Warning List (May not be present)**

❸ **Error/Warning Element(s) indicating:**

a. A sequence number

b. The section in which there is the wrong element

c. The element name to which the warning/error is referring to

d. The element value to which the warning/error is referring to

e. Describes if the comment reported is referring to an error or a warning

f. The class of error/warning that it is reported

g. A more detailed textual description of the warning/error

Structure of the Errors/Warning Elements for the Acknowledgement example described in Chapter 9.4.3:

a. 1-

b. In section DRUG

c. on field medicinalproduct (ICH E2B(R2) B.4.k.2.1)

d. value: PRODUCTEXAMPLE

e. reported Warning

f. BUSINESSRULES – LOOKUP

g. - CheckSub PRODUCTEXAMPLE must be a valid Medicinal Product;

❹ **Parsing Information:**

- Correct Report
- Report with Warnings
- Report with Errors

❺ **Classification information section (See Chapter 10, ICSR Classification)**

❻ **Current Report Classification:**

- Displays the EV report ID and the classification outcome

❼ **Old Report Classification:**

- Displays the EV report ID which was previously stored in the system, and the reclassification status of the previously stored report.

9.5.1. Field Level error description list

Summary of errors/warnings that may appear in an Acknowledgment Message:

9.5.1.1. Unexpected element

If the element 'xxx' is not expected in the document.
Reason: Element found is not expected according to the DTD Schema.

9.5.1.2. Enumeration List Error

If the element 'xxx' value is not part of a standard value list.
Enumeration constraint failed. The element <element name - E2B Ref.> has an invalid value according to its data type.

9.5.1.3. MaxInclusive Error

If the element 'xxx' value is exceeding the maximum value allowed.
MaxInclusive constraint failed. The element <element name - E2B Ref.> has an invalid value according to its data type.

9.5.1.4. MaxLength

If the element 'xxx' value's length is exceeding its maximum allowed.
MaxLength constraint failed. The element <element name - E2B Ref.> has an invalid value according to its data type.

9.5.1.5. MinInclusive Error

If the element 'xxx' value is smaller than the minimum value allowed.
MinInclusive constraint failed. The element <element name - E2B Ref.> has an invalid value according to its data type.

9.5.1.6. Datatype Error

If the element 'xxx' value type is not correct (i.e. a character instead of an integer).
The value is invalid according to its data type. The value of 'A' is invalid according to its data type. The element <element name - E2B Ref.> has an invalid value according to its data type.

9.5.1.7. totalDigit Error

If the element 'xxx' representing a decimal, exceeds the maximum number of admissible digits:
totalDigits constraint failed. The element <element name - E2B Ref.> has an invalid value according to its data type.

9.5.1.8. fractionDigit Error

If the element 'xxx', representing a decimal, exceeds the maximum number of digits in the fractional part:
fractionDigits constraint failed. The element <element name - E2B Ref.> has an invalid value according to its data type.

9.5.1.9. DateLength Error

If the element 'xxx', representing a date, has an unexpected number of digits:
Data Length not correct (Format: CCYYMMDD Value: 200212);

9.5.1.10. DateFormat Error

If the element value, that represents a date, does not correspond to the type specified in the corresponding dateformat element.
Date is not correct (Format: CCYYMMDD Value: 200212).

9.5.1.11. DateValid Error

If the element, that represents a date, has an invalid value.
Date is not a valid value: 20021313 Error: NOT a valid date.

9.5.1.12. LookupMedDRALLT Error

If the element value (i.e. 'xxx'), does not match with the MedDRA LLT lookup.
<xxx> must be a valid MedDRA term.

9.5.1.13. LookupProducts Error

If the element value (i.e. 'xxx'), does not match with the Medicinal Product lookup.
<xxx> must be a valid Medicinal Product.

9.5.1.14. LookupSubstance Error

If the element value (i.e. 'xxx') does not match with the Active Substance lookup.
<xxx> must be a valid activesubstance.

9.5.1.15. LookupDosageform Error

If the element value (i.e. 'xxx') does not match with the Dosage Form lookup.
<xxx> must be a valid dosageform.

9.5.1.16. LookupCountryCode Error

If the element value (i.e. 'xxx') does not match the Country Code lookup.
<xxx> must be a valid countrycode.

9.5.1.17. LookupLanguage Error

If the element value (i.e. 'xxx') does not match the Language lookup.
<xxx> must be a valid language.

9.5.1.18. LookupMedDRAversion Error

If the MedDRA version is not supported the following error is generated.
The requested MedDRA version is not supported in the target environment.

9.5.1.19. PreviousDate

If the element, that represents a date, indicates a future date.
NOT Valid Date: future date (05/04/50).

9.5.1.20. Startend

If the element, that represents an end date, is previous to the start date.
NOT Valid enddate. Enddate (20/01/01) must be greater than corresponding Startdate (22/01/01).

9.5.1.21. PatternFormation Error

The element value must be specified using a specific pattern e.g. XX–ABCDEFH-12345678 and the given value does not comply with this pattern.
The element referred must conform to the agreed format.

9.5.1.22. PatternConsituentValue Error

In an element that must be given in a pattern, one or more of the parts of the pattern is validated. This error indicates a failure in this validation e.g. country code element of the given 'Worldwide unique case identification number'.
The element referred must have valid values in each checked section of the acceptable data pattern.

9.5.2. Field Pair Error description list

9.5.2.1. ElementNull Error

If the element must be null as the value of another corresponding element requires this.
Since the element <element name aaa - E2B ref.> has the value <xxx>, the element <element name bbb - E2B ref.> cannot contain a value.

9.5.2.2. ElementValue

The element value must be specified as the value of another element requires it. This error is signalled when a MedDRA term has been specified but the corresponding MedDRA version field has been left empty.
Since the element <element name aaa - E2B ref.> has a value, the element <element name bbb - E2B ref.> must contain a value.

9.5.3. Section Level Error description list

These errors are all generated at the section level where multiple instances of the same section are used within the same report or where errors do not pertain to a single field.

9.5.3.1. ElementsNull Error

If the element must be null as the value of another corresponding element requires this.
Since the element patientsex – B.1.5 denotes 'male', these two elements cannot have a value (patientlastmenstrualdate - B.1.6b, lastmenstrualdateformat – B.1.6a).

9.5.3.2. AtMostOne Error

If at most one element can be present, but there is more than one element specified.
Only one of these elements can contain a value: authoritynumb, companynumb.

9.5.3.3. AtLeastOne Error

If one element between n-elements must be present, but no element is specified.
At least one of these elements must contain a value: authoritynumb, companynumb.

9.5.3.4. AtLeastOneSectionFieldValue Error

The element value must be present with a specific value given in at least one of the repeated sections. This error is generated when one section must have a particular drug characterisation.
The value <xxx> must be present in the element <element name - E2B Ref.> in one of the repeated sections.

9.5.3.5. AtLeastOneSectionFieldWithValue Error

The value in the field must be taken from a list of specific values in at least one of the repeated sections.

Since the element reporttype – A.1.4 has value 2, at least one of the primarysource – A.2 sections must have the field observestudytype – A.2.3.3 with value 1.

10. ICSR Classification

The classification is a process in which EV manages the versioning of the incoming ICSRs. The classification rules are designed to maintain a concept where the ICSRs, which are classified as Case Reports, describe the most recent information on a specific ICSR of a patient. In addition, the entire history of the case reports related to a specific ICSR is also maintained in the form of Replaced Reports. Further, an administrative process allows for maintenance of ICSRs which have been nullified by the original sender, indicating the reasons for the nullification of a case.

10.1. Case Classification

A report may be classified as:

- Case report
- Replaced report
- Error report
- Nullified report

10.1.1. Case Report

Case Report is a report describing a case for the first time (Initial report) or at a later time (Follow-up). It is the classification assigned to the most recent version of a case received by EV.

10.1.2. Replaced Report

Replaced Report is a case report superseded by a case report with a more recent receipt date based on the follow-up information or a case report nullified by a nullification report.

10.1.3. Error Report

Error Report is a report containing syntactic or semantic mistakes.

10.1.4. Nullified Report

Nullified Report is a report with the data element *casenullification* (ICH E2B(R2) A.1.13) set to 'yes'.

10.2. Classification algorithm

This chapter presents the classification algorithm based on the data element *casenullification* (ICH E2B(R2) A.1.13), as well as the case number (data elements *authoritynumb* (ICH E2B(R2) A.1.10.1) or *companynumb* (ICH E2B(R2) A.1.10.2)) and the data element *receiptdate* (ICH E2B(R2) A.1.7b):

10.2.1. New and Follow Up Reports

If the nullification field of loading report =0
case number of loading report <> case number of pre-existing report
--> Type of loading report =case report
case number of loading report = case number of pre-existing report and headquarter organisation ID of loading report = headquarter organisation ID of pre-existing report, the following applies
- if receipt date of loading report >= receipt date of pre-existing report

--> Type of loading report =case report
--> Type of pre-existing report =replaced report
- if receipt date of loading report < receipt date of pre-existing report
--> Type of loading report =replaced report

10.2.2. Nullification Reports

If the nullification field of loading report =1
case number of loading report <> case number of pre-existing report and headquarter organisation ID of loading report = headquarter organisation ID of pre-existing report
--> Type of loading report =error report
case number of loading report = case number of pre-existing report and headquarter organisation ID of loading report = headquarter organisation ID of pre-existing report, the following applies
- if receipt date of loading report >= receipt date of pre-existing report
--> Type of loading report =nullified report
--> Type of pre-existing report =replaced report
- if receipt date of loading report < receipt date of pre-existing report
--> Type of loading report =error report

The classification outcome is reported in the data element errormessagecomment (ICH M2 B.1.9) of the Report Acknowledgment section.

10.3. Master Cases

Duplicate cases are generally managed through a process of merging two-or-more cases into one Master Case. This process can consist of one of the following approaches:

- The Master Case can either be based on one of the existing cases, with information from the other subordinate duplicate case added unless the same, or more-precise, information is already present in the Master Case, or
- The Master Case can be created as a new case combining the information from the subordinate duplicate cases.

Regardless of the approach chosen, the Master Case should always contain all the case reference numbers from all subordinate duplicate cases, such that they can be easily traced. The Master Case should reflect the most accurate and up-to-date information available to the organisation. Guidance on duplicate management is available in the Draft-CHMP Guideline on Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs), Doc. Ref. EMA/13432/2009, under consultation.

11. Causality Assessment Reporting in ICSRs from Clinical Trials

11.1. Background on Causality Assessment in Clinical Trials

The provisions regarding the recording and the notification of serious adverse reactions, related to interventional clinical trials for which at least one site is located within the European Economic Area (EEA), are defined in Article 16 and 17 of the Clinical Trials Directive 2001/20/EC.

In accordance with Article 16 of the Clinical Trials Directive the sponsor shall keep detailed records of all adverse events which are reported to him by investigators.

Article 17 of the Clinical Trials Directive requires the sponsors to record and report on an expedited basis to the National Competent Authorities (NCAs) of the concerned Member States (MSs) all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) related to Investigational Medicinal Products (IMPs). In addition once a year, the sponsor of a clinical trial should provide NCAs with a report of all serious adverse reactions related to the IMP(s) which have occurred in the concerned clinical trials.

The Detailed Guidance ENTR/CT 3[10] recommends the investigator and the sponsor to evaluate the seriousness and the causality between the IMP and/or concomitant therapy and the adverse event. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the IMP (and/or concomitant therapy in case of suspicion of interaction with the IMP) should qualify as adverse reactions. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, both, the opinion of the investigator and the sponsor should be provided.

In accordance with the Detailed Guidance ENTR/CT 3, serious unexpected adverse reactions with a reasonable causal relationship to an IMP (and/or concomitant therapy in case of suspicion of interaction with the IMP) qualify as SUSARs and are subject to expedited reporting. Serious expected adverse reactions and non serious (expected and unexpected) adverse reactions suspected to be related to the IMP are not subject to expedited reporting. The same is also applicable for any adverse events and for any adverse reactions suspected to be related only to a medicinal product other than the IMP and for which there is no suspicion of interaction with the IMP. The Detailed Guidance defines other important safety issues (e.g. lack of efficacy of an IMP used for the treatment of a life-threatening disease) requiring expediting reporting and set out the reporting format for these specific issues which should be notified to the competent authority(ies) by a letter. They should not be sent electronically to the EudraVigilance Clinical Trial Module (EVCTM).

11.2. Current Issues Related to SUSARs Reporting

The Clinical Trials Directive 2001/20/EC and the Detailed Guidance ENTR/CT 3 provide provisions to sponsors regarding the expedited reporting of SUSARs. However, in practice, Individual Case Safety Reports (ICSRs) submitted to the NCAs and to EVCTM often also contain events or reactions which do not qualify as SUSAR but which may just be associated to the conduct of the clinical trial or to a medicinal product other than the IMP and for which there is no suspicion of interaction with the IMP.

[10] Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, April 2006, Revision 2

11.3. New Validation Rules

To facilitate and to improve the monitoring of SUSARs, it is important to systematically identify in ICSRs reactions related to the IMP(s). Therefore the provision of causality assessments becomes mandatory for all reported events/reactions against all reported medicinal products classified as suspect or interacting. This is applicable only to ICSRs (initial and follow-up reports) submitted prospectively to EVCTM. No validation on the provision of causality assessments is conducted on ICSRs submitted to the EudraVigilance Post-Authorisation Module (EVPM).

The reporting to EVCTM applies to cases of SUSARs occurring in clinical trials. Therefore at least one of the reported medicinal products classified as suspect or interacting should be an IMP of the corresponding clinical trial.

The new validation rules of ICSRs submitted to EVCTM are based on the following principle:

- For each reported event/reaction a causality assessment should be provided by the Investigator AND/OR by the Sponsor against any of the medicinal products reported as suspect or interacting. If this information is not available, the ICSR is classified as an error report and requires correction and resubmission.
- Any initial ICSR should contain at least one reaction with a causality assessment 'Reasonable possibility' (based on the binary decision method detailed in the CIOMS Working Group VI report[11]) to at least one of the reported medicinal products classified as suspect or interacting. If this information is not available, the ICSR submitted to EVCTM is classified as an error report and requires correction and resubmission if applicable. This rule is not applied to follow-up ICSRs submitted to EVCTM in order to allow to sponsors the possibility to downgrade the causality of an initial ICSR.

The causality information should be reported in the repeatable section Relatedness of Drug to Reaction(s)/Event(s) (ICH E2B(R2) B.4.k.18) in accordance with the recommendations summarised in the Appendixes A and C.

These new validation processes will become mandatory from the date of the technical implementation (07 February 2011) of the revised business rules in EudraVigilance as outlined in the detailed Implementation Plan dated 15 October 2010 (Doc. Ref. EMA/665231/2008 – Revision 1).

[11] Management of Safety Information from Clinical Trials CIOMS Working Group VI (CIOMS, Geneva 2005).

Appendix A: Business Rules (Error Generation)

Table Legend:

Data Element: Element (or section) standard code

Name: Element (or section) standard name

Max Length: Maximum number of characters for an element

Type: Element type
- *AN --> Alphanumeric*
- *N --> Numeric*

Values: List of admissible values (if its exists)
- *(…) --> list of values*
- *[…] --> interval of values*
- *Lookup on…. --> value is contained in a database*
- *Date --> see Note 9*
- *X.X --> MedDRA version*

Mandatory: Indicates that Element (or section) is mandatory (if nothing is specified, it is considered optional)
- *If specified (1... ∞), this means that there can be multiple iterations of the element or section*

Notes: Other information
- *WARNING means that failure on this rule generates a warning (not an error)*
- *A Safety Message should explicitly reference DTD version 2.1 published on the EudraVigilance web site (Refer to Chapter 4 for generating a valid Safety Message)*
- *<ichicsr> element should have a 'lang' attribute (mandatory) set to a valid ISO639 code*
- *All other elements may have a 'lang' attribute (optional) set to a valid ISO639 code*
- *All reported country names should be valid ISO3166 country codes (except in ICH E2B B.5 section 'Narrative case summary and further information'). Use of non-valid ISO3166 country code generates an error message in the validation process.*

A.1 Business Rules applicable to EVPM and/or EVCTM (Error Generation)

Table 2 summarises the list of the business rules generating error messages by EV in case of non-compliance. This is the list of all rules generating error messages. For the list of rules applicable to EVPM exclusively or EVCTM exclusively refer to Section A.2 or A.3 respectively.

Table 2. List of all business rules generating error messages

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
M.1	**ichicsrmessageheader**				**Mandatory**	
M.1.1	messagetype	16	AN	(ichicsr, backlog, backlogct, psur, ctasr)	Mandatory	See note 16
M.1.2	messageformatversion	3	AN	(2.1)	Mandatory	
M.1.3	messageformatrelease	3	AN	(1, 1.0, 2, 2.0)	Mandatory	
M.1.4	Messagenumb	100	AN		Mandatory	
M.1.5	messagesenderidentifier	60	AN		Mandatory	

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
M.1.6	messagereceiveridentifier	60	AN		Mandatory	See note 14
M.1.7a	messagedateformat	3	N	(204)	Mandatory	See note 9
M.1.7b	Messagedate	14	N	Date	Mandatory	Should conform to M.1.7a. See note 10
A.1	**Safetyreport**				**Mandatory**	**(1...∞)**
A.1.0.1	safetyreportid	100	AN	(valid ISO3166 country code-regulator or company name-report number)	Mandatory	
A.1.1	primarysourcecountry	2	A	Lookup on ISO3166	Mandatory	See note 4
A.1.2	occurcountry	2	A	Lookup on ISO3166		See note 4
A.1.3a	transmissiondateformat	3	N	(102)	Mandatory	See note 9
A.1.3b	transmissiondate	8	N	Date	Mandatory	Should conform to A.1.3a. See note 10
A.1.4	Reporttype	1	N	[1-4] 1=Spontaneous 2=Report from study 3=Other 4=Not available to sender (unknown)	Mandatory	See note 2
A.1.5.1	Serious	1	N	(1,2) 1=Yes 2=No	Mandatory. See note 18	Accepted value is (1) if one of A.1.5.2 values is (1)
A.1.5.2	seriousnessdeath	1	N	(1,2) 1=Yes 2=No	If A.1.5.1 value is (1), at least one of the values should be (1). See note 18	See note 6
	seriousnesslifethreatening	1	N	(1,2) 1=Yes 2=No		
	seriousnesshospitalization	1	N	(1,2) 1=Yes 2=No		
	seriousnessdisabling	1	N	(1,2) 1=Yes 2=No		
	Seriousnesscongenitalanomali	1	N	(1,2) 1=Yes 2=No		
	seriousnessother	1	N	(1,2) 1=Yes 2=No		
A.1.6a	receivedateformat	3	N	(102)	Mandatory	See note 9
A.1.6b	receivedate	8	N	Date	Mandatory	Should be ≤ to A.1.7b and should conform to A.1.6a. See note 10
A.1.7a	receiptdateformat	3	N	(102)	Mandatory	See note 9
A.1.7b	receiptdate	8	N	Date	Mandatory	Should be ≥ to A.1.6b and should conform to A.1.7a. See note 10
A.1.8.1	additionaldocument	1	N	(1,2) 1=Yes 2=No		
A.1.9	fulfillexpeditecriteria	1	N	(1,2) 1=Yes 2=No		
A.1.10.1	authoritynumb	100	AN	(valid ISO3166 country code-regulator name-report number)	Mandatory	One of A.1.10.1 or A.1.10.2 accepted See note 3
A.1.10.2	companynumb	100	AN	(valid ISO3166 country code-company name-report number)		
A.1.11	duplicate	1	N	(1)		

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
				1=Yes		
A.1.13	casenullification	1	N	(1) 1=Yes		See note 17
A.1.14	Medicallyconfirm	1	N	(1,2) 1=Yes 2=No		
A.2	**primarysource**				**Mandatory**	**(1...∞)**
A.2.1.1d	reporterfamilyname	50	AN			At least one of A.2.1.1d, A.2.1.2a, A.2.1.2f, A.2.1.3, A.2.2, A.2.3.1
A.2.1.2a	reporterorganization	60	AN			At least one of A.2.1.1d, A.2.1.2a, A.2.1.2f, A.2.1.3, A.2.2, A.2.3.1
A.2.1.2e	reporterstate	40	AN		Mandatory for cases originating in Spain (one of A.2.1.2e or A.2.1.2f)	See note 25
A.2.1.2f	reporterpostcode	15	AN		Mandatory for cases originating in Spain (one of A.2.1.2e or A.2.1.2f)	At least one of A.2.1.1d, A.2.1.2a, A.2.1.2f, A.2.1.3, A.2.2, A.2.3.1 See note 25
A.2.1.3	reportercountry	2	A	Lookup on ISO3166		At least one of A.2.1.1d, A.2.1.2a, A.2.1.2f, A.2.1.3, A.2.2, A.2.3.1
A.2.1.4	qualification	1	N	[1-5] 1=Physician 2=Pharmacist 3=Other Health Professional 4=Lawyer 5=Consumer or other non health professional	Mandatory	See note 19
A.2.2	literaturereference	500	AN			At least one of A.2.1.1d, A.2.1.2a, A.2.1.2f, A.2.1.3, A.2.2, A.2.3.1
A.2.3.1	studyname	100	AN		Mandatory for any transmission to EVCTM	At least one of A.2.1.1d, A.2.1.2a, A.2.1.2f, A.2.1.3, A.2.2, A.2.3.1. See notes 7 and 11
A.2.3.2	sponsorstudynumb	35	AN		Mandatory for any transmission to EVCTM	See note 11
A.2.3.3	observestudytype	1	N	(1,2,3) 1=Clinical trials 2=Individual patient use 3=Other studies	Mandatory if A.1.4 value is (2).	See notes 2 and 11
A.3.1	**sender**				**Mandatory**	
A.3.1.1	sendertype	1	N	[1-6] 1=Pharmaceutical Company 2=Regulatory Authority 3=Health professional 4=Regional Pharmacovigilance Center 5=WHO Collaborating		

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
				Center for International Drug Monitoring 6=Other		
A.3.1.2	senderorganization	60	AN		Mandatory	
A.3.1.4e	sendercountrycode	2	A	Lookup on ISO3166		
A.3.1.4g	sendertelextension	10	AN			See note 13 (warning/error)
A.3.1.4j	senderfaxextension	10	AN			See note 13 (warning/error)
A.3.2	**receiver**				**Mandatory**	
A.3.2.1	receivertype	1	N	(1,2,4,5,6) 1=Pharmaceutical Company 2=Regulatory Authority 3=Health professional 4=Regional Pharmacovigilance Center 5=WHO Collaborating Center for International Drug Monitoring 6=Other		
A.3.2.2a	receiverorganisation	60	AN		Mandatory	
A.3.2.3e	receivercountrycode	2	A	Lookup on ISO3166		
A.3.2.3g	receivertelextension	10	AN			See note 13 (warning/error)
A.3.2.3j	receiverfaxextension	10	AN			See note 13 (warning/error)
B.1	**patient**				**Mandatory**	
B.1.1	patientinitial	10	AN			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5
B.1.1.1a	patientgpmedicalrecordnumb	20	AN			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5
B.1.1.1b	patientspecialistrecordnumb	20	AN			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5
B.1.1.1c	patienthospitalrecordnumb	20	AN			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5
B.1.1.1d	patientinvestigationnumb	20	AN			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a -

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
						B.1.2.2.1a - B.1.2.3 - B.1.5
B.1.2.1a	patientbirthdateformat	3	N	(102)	Mandatory if B.1.2.b is not Null	See note 9
B.1.2.1b	patientbirthdate	8	N	Date		At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 - B.1.5. Should conform to B.1.2.1a. See note 10
B.1.2.2a	patientonsetage	5	N			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 - B.1.5. If not NULL, should not be > 150 years. See note 5
B.1.2.2b	patientonsetageunit	3	N	[800-805]	Mandatory if B.1.2.2a is not NULL	See note 26
B.1.2.2.1a	gestationperiod	3	N			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 - B.1.5
B.1.2.2.1b	gestationperiodunit	3	N	(802,803,804,810)	Mandatory if B.1.2.2.1a is not NULL	See note 26
B.1.2.3	patientagegroup	1	N	[1-6] 1=Neonate 2=Infant 3=Child 4=Adolescent 5=Adult 6=Elderly		At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 - B.1.5
B.1.3	patientweight	6	N			If not null, should not be > 650 kg. See note 5
B.1.4	patientheight	3	N			If not null, should not be > 250 cm. See note 5
B.1.5	patientsex	1	N	(1,2) 1=Male 2=Female		At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 - B.1.5
B.1.6a	lastmenstrualdateformat	3	N	(102,610,602)	Mandatory if B.1.6b not NULL	Should be NULL if B.1.5 value is (1) (patient is male). See note 9
B.1.6b	patientlastmenstrualdate	8	N	Date		Should conform to B.1.6a. Should be NULL if B.1.5 value is (1) (patient is male). See note 10

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
B.1.7.1a.1	patientepisodenamemeddraversion	8	AN	x.x	Mandatory if B.1.7.1a.2 is not NULL.	See note 1
B.1.7.1a.2	patientepisodename	250	N	Lookup on MedDRA LLT		See note 1
B.1.7.1b	patientmedicalstartdateformat	3	N	(102,610,602)	Mandatory if B.1.7.1c not NULL	See note 9
B.1.7.1c	patientmedicalstartdate	8	N	Date		Should precede B.1.7.1f and conform to B.1.7.1b. See note 10
B.1.7.1d	patientmedicalcontinue	1	N	(1,2,3) 1=Yes 2=No 3=Unknown		
B.1.7.1e	patientmedicalenddateformat	3	N	(102,610,602)	Mandatory if B.1.7.1f not NULL	See note 9
B.1.7.1f	patientmedicalenddate	8	N	Date		Should follow B.1.7.1c and conform to B.1.7.1e. See note 10
B.1.8b	patientdrugstartdateformat	3	N	(102,610,602)	Mandatoy if B.1.8c not NULL	See note 9
B.1.8c	patientdrugstartdate	8	N	Date		Should precede B.1.8e and conform to B.1.8b. See note 10
B.1.8d	patientdrugenddateformat	3	N	(102,610,602)	Mandatory if B.1.8e not NULL	See note 9
B.1.8e	patientdrugenddate	8	N	Date		Should follow B.1.8c and conform to B.1.8d. See note 10
B.1.8f.1	patientindicationmeddraversion	8	AN	x.x	Mandatory if B.1.8f.2 is not NULL.	See note 1
B.1.8f.2	patientdrugindication	250	N	Lookup on MedDRA LLT		See note 1
B.1.8g.1	patientdurgreactionmeddraversion	8	AN	x.x	Mandatory if B.1.8g.2 is not NULL.	See note 1
B.1.8g.2	patientdrugreaction	250	N	Lookup on MedDRA LLT		See note 1
B.1.9.1a	patientdeathdateformat	3	N	(102,610,602)	Mandatory if B.1.9.1b not NULL	See note 9
B.1.9.1b	patientdeathdate	8	N	Date		Should conform to B.1.9.1a. See note 10
B.1.9.2.a	patientdeathreportmeddraversion	8	AN	x.x	Mandatory if B.1.9.2.b is not NULL.	See note1
B.1.9.2.b	patientdeathreport	250	N	Lookup on MedDRA LLT		See note 1
B.1.9.3	patientautopsyyesno	1	N	(1,2,3) 1=Yes 2=No 3=Unknown		
B.1.9.4a	patientdetermautopsmeddraversion	8	AN	x.x	Mandatory if B.1.9.4b is not NULL.	See note 1
B.1.9.4b	patientdetermineautopsy	250	N	Lookup on MedDRA LLT		See note1

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
B.1.10.2.1a	parentbirthdateformat	3	N	(102)	Mandatory if B.1.10.2.1b not NULL	See note 9
B.1.10.2.1b	parentbirthdate	8	N	Date		Should conform to B.1.10.2.1a. See note 10
B.1.10.2.2a	parentage	2	N			See note 5
B.1.10.2.2b	parentageunit	3	N	(801)	Mandatory if B.1.10.2.2a is not NULL	See note 26
B.1.10.3a	parentlastmenstrualdateformat	3	N	(102)	Mandatory if B.1.10.3b not NULL	Should be NULL if B.1.10.6 value is (1) (parent is male). See note 9
B.1.10.3b	parentlastmenstrualdate	8	N	Date		Should conform to B.1.10.3a. Should be NULL if B.1.10.6 value is (1) (parent is male). See note 10
B.1.10.4	parentweight	6	N			If not null, should not be > 650 kg. See note 5
B.1.10.5	parentheight	3	N			If not null, should not be > 250 cm. See note 5
B.1.10.6	parentsex	1	N	(1,2) 1=Male 2=Female		
B.1.10.7.1a.1	parentmedicalepisodemeddraversion	8	AN	x.x	Mandatory if B.1.10.7.1a.2 is not NULL.	See note 1
B.1.10.7.1a.2	parentmedicalepisodename	250	N	Lookup on MedDRA LLT		See note 1
B.1.10.7.1b	parentmedicalstartdateformat	3	N	(102,610,602)	Mandatory if B.1.10.7.1c not NULL	See note 9
B.1.10.7.1c	parentmedicalstartdate	8	N	Date		Should precede B.1.10.7.1f and conform to B.1.10.7.1b. See note 10
B.1.10.7.1d	parentmedicalcontinue	1	N	(1,2,3) 1=Yes 2=No 3=Unknown		
B.1.10.7.1e	parentmedicalenddateformat	3	N	(102,610,602)	Mandatory if B.1.10.7.1f not NULL	See note 9
B.1.10.7.1f	parentmedicalenddate	8	N	Date		Should follow B.1.10.7.1c and conform to B.1.10.7.1e. See note 10
B.1.10.8b	parentdrugstartdateformat	3	N	(102,610,602)	Mandatory if B.1.10.8c not NULL	See note 9
B.1.10.8c	parentdrugstartdate	8	N	Date		Should precede B.1.10.8e and conform to B.1.10.8b. See note 10
B.1.10.8d	parentdrugenddateformat	3	N	(102,610,602)	Mandatory if B.1.10.8e not NULL	See note 9
B.1.10.8e	parentdrugenddate	8	N	Date		Should follow B.1.10.8c and conform to

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
						B.1.10.8d. See note 10
B.1.10.8f.1	parentdrugindication meddraversion	8	N	x.x	Mandatory if B.1.10.8f.2 is not NULL	See note 1
B.1.10.8f.2	parentdrugindication	250	N	Lookup on MedDRA LLT		See note 1
B.1.10.8g.1	parentdrugreactionmeddraversion	8	AN	x.x	Mandatory if B.1.10.8g.2 is not NULL.	See note 1
B.1.10.8g.2	parentdrugreaction	250	N	Lookup on MedDRA LLT		See note1
B.2	**reaction**				**Mandatory**	**(1...∞)**
B.2.i.1.a	reactionmeddraversionllt	8	AN	x.x	Mandatory	See note 1
B.2.i.1.b	reactionmeddrallt	250	N	Lookup on MedDRA LLT	Mandatory	See note 1
B.2.i.2.a	reactionmeddraversionpt	8	AN	x.x	Mandatory if B.2.i.2.b is not NULL.	See note 1
B.2.i.3	termhighlighted	1	N	(1,2,3,4) 1=Yes, highlighted by the reporter, NOT serious 2=No, not highlighted by the reporter, NOT serious 3=Yes, highlighted by the reporter, SERIOUS 4=No, not highlighted by the reporter, SERIOUS		
B.2.i.4a	reactionstartdateformat	3	N	(102,203,610,602)	Mandatory if B.2.i.4b not NULL	See note 9
B.2.i.4b	reactionstartdate	12	N	Date		Should precede B.2.i.5b and conform to B.2.i.4a. See note 10
B.2.i.5a	reactionenddateformat	3	N	(102,203,610,602)	Mandatory if B.2.i.5b not NULL	See note 9
B.2.i.5b	reactionenddate	12	N	Date		Should follow B.2.i.4b and conform to B.2.i.5a. See note 10
B.2.i.6b	reactiondurationunit	3	N	[801-807]	Mandatory if B.2.i.6a is not NULL	See note 26
B.2.i.7.1b	reactionfirsttimeunit	3	N	[801-807]	Mandatory if B.2.i.7.1a is not NULL	See note 26
B.2.i.7.2b	reactionlasttimeunit	3	N	[801-807]	Mandatory if B.2.i.7.2a is not NULL	See note 26
B.2.i.8	reactionoutcome	1	N	[1-6] 1=recovered/ resolved 2=recovering/ resolving 3=not recovered/ not resolved 4=recovered/	Mandatory	At least one of B.2.i.8 should contain the value (5) if A.1.5.2 seriousnessdeath value is (1). See note 6

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
				resolved with sequelae 5=fatal 6=unknown		
B.3	**test**					
B.3.1a	testdateformat	3	N	(102,610,602)	Mandatory if B.3.1b not NULL	See note 9
B.3.1b	testdate	8	N	Date		Should conform to B.3.1a. See note 10
B.3.1c	testname	100	N	Lookup on MedDRA LLT		See note 15
B.3.1.3	moreinformation	1	N	(1,2) 1=Yes 2= No		
B.4	**drug**				**Mandatory**	**(1...∞)**
B.4.k.1	drugcharacterization	1	N	(1,2,3) 1=Suspect 2=Concomitant 3=Interacting	Mandatory	At least one of B.4.k.1 values should be (1) or (3)
B.4.k.2.1	medicinalproduct	70	AN	Lookup on Medicinal Products (warning)		At least one of B.4.k.2.1-B.4.k.2.2 (error). See note 12
B.4.k.2.2	activesubstancename	100	AN	Lookup on Substances (warning)	Mandatory for any transmission to EVCTM (error) or EVPM (warning) when the value in B.4.k.1 is (1) or (3)	At least one of B.4.k.2.1 and B.4.k.2.2 (error). See note 12
B.4.k.2.3	obtaindrugcountry	2	A	Lookup on ISO3166		
B.4.k.4.2	drugauthorizationcountry	2	A	Lookup on ISO3166		
B.4.k.5.2	drugstructuredosageunit	3	N	[001-032]	Mandatory if B.4.k.5.1 is not NULL	See note 26
B.4.k.5.5	drugintervaldosagedefinition	3	N	(801,802,803,804,805,806,807,810,811,812,813)		See note 26
B.4.k.5.7	drugcumulativedosageunit	3	N	[001-032]	Mandatory if B.4.k.5.6 is not NULL	See note 26
B.4.k.10b	reactiongestationperiodunit	3	N	(802,803,804,810)	Mandatory if B.4.k.10a is not NULL	See note 26
B.4.k.11a	drugindicationmeddraversion	8	AN	x.x	Mandatory if B.4.k.11b is not NULL	See note 1
B.4.k.11b	drugindication	250	N	Lookup on MedDRA LLT		See note 1
B.4.k.12a	drugstartdateformat	3	N	(102,610,602)	Mandatory if B.4.k.12b not NULL	See note 9
B.4.k.12b	drugstartdate	8	N	Date		Should precede B.4.k.14b and conform to B.4.k.12a. See note 10
B.4.k.13.1b	drugstartperiodunit	3	N	[801-807]	Mandatory if B.4.k.13.1a is not NULL	See note 26
B.4.k.13.2b	druglastperiodunit	3	N	[801-807]	Mandatory if	See note 26

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
					B.4.k.13.2a is not NULL	
B.4.k.14a	drugenddateformat	3	N	(102,610,602)	Mandatory if B.4.k.14b not NULL	See note 9
B.4.k.14b	drugenddate	8	N	Date		Should follow B.4.k.12b and conform to B.4.k.14a. See note 10
B.4.k.15b	drugtreatmentdurationunit	3	N	[801-806]	Mandatory if B.4.k.15a is not NULL	See note 26
B.4.k.16	actiondrug	1	N	(1,2,3,4,5,6) 1=Drug withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Unknown 6=Not applicable		
B.4.k.17.1	drugrecurreadministration	1	N	(1,2,3) 1=Yes 2= No 3 = Unknown		
B.4.k.17.2a	drugrecuractionmeddraversion	8	AN	x.x	Mandatory if B.4.k.17.2b is not NULL.	See note 1
B.4.k.17.2b	drugrecuraction	250	N	Lookup on MedDRA LLT	Mandatory if the section drugrecurrence is specified.	See notes 1 and 8
B.4.k.18	**drugreactionrelatedness**					**(0...∞)** **See note 20**
B.4.k.18.1a	drugreactionassesmeddraversion	8	AN	x.x	Mandatory if B.4.k.18.1b is not NULL. Mandatory for any transmission to EVCTM for any medicinal product with B.4.k.1 values = (1) *suspect* or (3) *interacting*	It should be the same as B.2.i.2.a. See note 1 and 21
B.4.k.18.1b	drugreactionasses	250	N	Lookup on MedDRA LLT	Mandatory for any transmission to EVCTM for any medicinal product with B.4.k.1 values = (1) *suspect* or (3) *interacting*	It should be the same as one specified in B.2.i.1.b. For transmission to EVCTM, it should be the same as any one of the codes specified in B.2.i.1.b. See note 1 and 21
B.4.k.18.2	drugassessmentsource	60	AN			The accepted value is (1) or (2) or (3) when the value in B.4.k.18.3 is (EVCTM). See note 22
B.4.k.18.3	drugassessmentmethod	35	AN			For transmission to EVCTM, at least one of B.4.k.18.3 values for each event/reaction

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
						should be (EVCTM). See note 23
B.4.k.18.4	drugresult	35	AN			For transmission to EVCTM, the accepted value is (1) or (2) when the value in B.4.k.18.3 is (EVCTM). See note 24
B.5.3a	senderdiagnosismeddraversion	8	AN	x.x	Mandatory if B.5.3b is not NULL.	See note 1
B.5.3b	senderdiagnosis	250	N	Lookup on MedDRA LLT		See note 1

A.2 Rules applicable to EVPM only (Error Generation)

Table 3 summarises the list of the business rules applicable to EVPM exclusively, generating error messages by EV in case of non-compliance.

Table 3. List of all business rules generating error messages applicable to EVPM exclusively

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
A.1.4	Reporttype	1	N	(1,2,3,4) 1=Spontaneous 2=Report from study 3=Other 4=Not available to sender (unknown)	Mandatory	See note 2
A.1.5.2	seriousnessdeath	1	N	(1,2) 1=Yes 2=No	If A.1.5.1 value is (1), at least one of the values should be (1). See note 18	Accepted value is (1) for seriousnessdeath criterion if one of B.2.i.8 value is (5). See note 6
A.2.3.3	Observestudytype	1	N	(2,3) 2=Individual patient use 3=Other studies	Mandatory if A.1.4 value is (2).	See notes 2

A.3 Rules applicable to EVCTM only (Error Generation)

Table 4 summarises the list of the business rules applicable to EVCTM exclusively, generating error messages by EV in case of non-compliance.

Table 4. List of all business rules generating error messages applicable to EVCTM exclusively

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
A.1.4	reporttype	1	N	(2) 2=Report from study	Mandatory	See note 2
A.2	**primarysource**				**Mandatory**	**(1...∞)** See note 11
A.2.3.1	studyname	100	AN		Mandatory	See notes 7 and 11
A.2.3.2	sponsorstudynumb	35	AN		Mandatory	See note 11
A.2.3.3	observestudytype	1	N	(1) 1=Clinical trials	Mandatory	See notes 2 and 11
B.4.k.2.2	activesubstancename	100	AN	Lookup on	Mandatory for	At least one of

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
				Substances (warning)	any transmission to EVCTM (error) when the value in B.4.k.1 is (1) or (3)	B.4.k.2.1 and B.4.k.2.2 (error). See note 12
B.4.k.18	**drugreactionrelatedness**					**(1...∞) See note 20**
B.4.k.18.1a	drugreactionassesmeddraversion	8	AN	x.x	Mandatory if B.4.k.18.1b is not NULL. Mandatory for any transmission to EVCTM for any medicinal product with B.4.k.1 values = (1) *suspect* or (3) *interacting*	It should be the same as B.2.i.2.a. See note 1 and 21
B.4.k.18.1b	drugreactionasses	250	N	Lookup on MedDRA LLT	Mandatory for any transmission to EVCTM for any medicinal product with B.4.k.1 values = (1) *suspect* or (3) *interacting*	For transmission to EVCTM, it should be the same as any one of the codes specified in B.2.i.1.b. See note 1 and 21
B.4.k.18.2	drugassessmentsource	60	AN			The accepted value is (1) or (2) or (3) when the value in B.4.k.18.3 is (EVCTM). See note 22
B.4.k.18.3	drugassessmentmethod	35	AN			For transmission to EVCTM, at least one of B.4.k.18.3 values for each event/reaction should be (EVCTM). See note 23
B.4.k.18.4	drugresult	35	AN			For transmission to EVCTM, the accepted value is (1) or (2) when the value in B.4.k.18.3 is (EVCTM). See note 24

A.4 Notes:

1. **MedDRA Version**

The supported MedDRA versions are related to the EV environment (EV compliance testing environment or production environment) that is the target of the Safety Message transmission. It also relates to the current MedDRA version officially published by the MedDRA Maintenance Support Service Organisation (MSSO). The EV compliance testing environment supports MedDRA version 4.0 and higher. The EV production environment supports the previous and the current MedDRA version. The validation process of the ICSRs accepts only current lower level term (LLT) numeric codes of the supported MedDRA versions. All stakeholders should follow the recommendations of the MedDRA MSSO regarding the switch to a new MedDRA version. The latest supported MedDRA versions in line with the official semi annual releases are posted on the EudraVigilance website. The use of non-valid numeric

MedDRA LLT codes generates an error message in the validation process (except in the data element *testname* (ICH E2B(R2) B.3.1c) where valid MedDRA LLT names are also accepted).

For the ICSRs to be transmitted as part of the retrospective population of EudraVigilance and for the periodic transmission of ICSRs, as outlined in Part III of Volume 9A of The Rules Governing Medicinal Products in the European Union, the fields requiring MedDRA coding will accept LLT numeric codes of MedDRA version 4.0 or higher.

2. ***reporttype* and *observestudytype***

Any transmissions to EV (EVPM or EVCTM) require the data element *reporttype* (ICH E2B(R2) A.1.4) and the data element *observestudytype* (ICH E2B(R2) A.2.3.3) to be correctly specified, as described in Appendixes A.2 and A.3, in order to obtain a successful outcome of the validation of the ICSRs. Failure of the validation generates an error message.

a) For ICSRs sent to EVPM:

- When the value of the data element *reporttype* (ICH E2B(R2) A.1.4) is '2' (report from study), the data element *observestudytype* (ICH E2B(R2)A.2.3.3) should not be NULL and the accepted values are '2' (individual patient use) or '3' (other studies).
- When the value of the data element *observestudytype* (ICH E2B(R2) A.2.3.3) is '2' (individual patient use) or '3' (other studies), the accepted value for the data element *reporttype* (ICH E2B(R2) A.1.4) is '2' (report from study).
- *Primarysource* (ICH E2B(R2) A.2) iterations are repeatable sections. Therefore, when mandatory, the data element *observestudytype* (ICH E2B(R2) A.2.3.3) needs to be specified in at least one section.

b) For SUSARs sent to EVCTM:

- The accepted value for the data element *reporttype* (ICH E2B(R2) A.1.4) is '2' (report from study). The data element *observestudytype* (ICH E2B(R2)A.2.3.3) should not be NULL and the accepted value is '1' (clinical trial).

When follow-up information impacts on the type of report or the type of study, the report should always be reclassified with the most specific information. For example,

- When an ICSR is initially submitted with the value '1' (spontaneous report) in the data element *reporttype* (ICH E2B(R2) A.1.4), it should be reclassified with the value '2' (report from study) if this information is available in the follow-up report and the data element *observestudytype* (ICH E2B(R2)A.2.3.3) should be populated with the appropriate value.
- When an ICSR is initially submitted to EVPM with the value '2' (individual patient use) or '3' (other studies) in the data element *observestudytype* (ICH E2B(R2)A.2.3.3), it should be reclassified with the value '1' (clinical trial) if this information is available in the follow-up report. The corresponding follow-up ICSR should be submitted to EVCTM. No nullification of the initial report should be done in EVPM.

3. ***companynum* and *authoritynumb***

There should be only one of these 2 data elements *authoritynumb* (ICH E2B(R2) A.1.10.1) or *companynumb* (ICH E2B(R2) A.1.10.2) provided in each report. The system generates an error if none of these data element or both of them are populated. The value in these data elements should be a concatenation of 'primary source country code-company or regulator name-report number'. Each component should be separated by a hyphen. The value should always start with a 'valid ISO3166 country code-'. Failure of the validation of the first part of the concatenation ('valid ISO3166 country

code-') generates an error message. Any information concerning previous transmissions of the same case from other senders should be provided in the section Other case identifiers in previous transmissions (ICH E2B(R2) A.1.11) where applicable.

4. ***primarysourcecountry* and *occurcountry***

The primary source country reported in the data element (ICH E2B(R2) A.1.1) is the country of the main primary source who reports the fact. It should correspond to one of the primary source countries reported in the data element *reportercountry* (ICH E2B(R2) A.2.1.3). All the *primarysource* (ICH E2B(R2) A.2) iterations are repeatable to allow entry of information for several reporters. For cases described in the world-wide literature, the country of the first author of the literature article should be used as the primary source country. In case the country of occurrence is different from the primary source country, this should be entered in the data element *occurcountry* (ICH E2B(R2) A.1.2).

5. **patient/parent's age, height or weight**

If the patient/parent's age, height or weight value is above the allowed upper limit, the relevant ICH E2B(R2) data element should remain empty and the information should be reported in the data element *narrativeincludeclinical* (ICH E2B(R2) B.5.1). Reported values above the upper limits generate an error message.

6. ***seriousnessdeath* and *reactionoutcome***

Any ICSR submitted to EVPM and EVCTM with the seriousness criterion 'results in death' (value '1' in the data element *seriousnessdeath* (ICH E2B(R2) A.1.5.2)) should have at least one reaction with an outcome 'fatal' (value '5' in the data element *reactionoutcome* (ICH E2B(R2) B.2.i.8)).

Failure of this validation will generate an error message.

Any ICSR submitted to EVPM with at least one reaction with the outcome 'fatal' (value '5' in the data element *reactionoutcome* (ICH E2B(R2) B.2.i.8)), should have the seriousness criterion 'results in death' populated with the value '1' (yes) in the data element *seriousnessdeath* (ICH E2B(R2) A.1.5.2). This validation does not apply to EVCTM.

If the death is unrelated to the reported reaction(s), only the section *patientdeath* (ICH E2B(R2) B.1.9) should be completed. The outcome of the reaction(s) reported in the data element *reactionoutcome* (ICH E2B(R2) B.2.i.8) should not be 'fatal' and the seriousness criterion in the data element (ICH E2B(R2) A.1.5.2) should not be flagged as 'results in death'.

7. ***studyname***

For any transmission to EVCTM, the data element *studyname* (ICH E2B(R2) A.2.3.1) should contain the following concatenations:

a) For SUSARs originating within the EEA:

- 'Valid EudraCT Number#Study abbreviated name' when the values in the data elements *primarysourcecountry* (ICH E2B(R2) A.1.1) and *occurcountry* (ICH E2B(R2) A.1.2) are EEA countries. Failure to enter a EudraCT Number validated against the EudraCT database will generate an error message.

b) For SUSARs originating outside the EEA:

- 'Valid EudraCT Number#Study abbreviated name' (if the clinical trial is authorised in the EEA or is contained in an agreed Paediatric Investigation Plan) or
- '#Study abbreviated name' (if the clinical trial is conducted exclusively outside the EEA or is not contained in an agreed Paediatric Investigation Plan),

when the values in the data elements *primarysourcecountry* (ICH E2B(R2) A.1.1) and *occurcountry* (ICH E2B(R2) A.1.2) are non-EEA countries.

A valid EudraCT Number should match with an authorised number in the EudraCT database and should have the format YYYY-NNNNNN-CC, where

- YYYY is the year in which the number has been issued,
- NNNNNN is a six digit sequential number,
- CC is a check digit.

The following generic EudraCT Number is provided for all interventional clinical trials including a centre in a Member State and started before 01 May 2004 (or before the clinical trial Directive 2001/20/EC has been implemented in a Member State): **EVCT-000000-16.** It should be used in the data element *studyname* (ICH E2B(R2) A.2.3.1) for these interventional clinical trials only. It should be followed by the '#' symbol and the study abbreviated name.

ICSRs originating from interventional clinical trials, which need to be reported by MAHs to EVCTM in accordance with the requirements described in Volume 9A of the Rules Governing Medicinal Products in the European Union, should include the following generic EudraCT number **EVCT-999999-25**, followed by the '#' symbol and the study abbreviated name. This is to be able to exclude these ICSRs from the 7 days expedited reporting compliance monitoring. It should be used in the data element *studyname* (ICH E2B(R2) A.2.3.1 for cases which occurred outside the EEA in interventional clinical trials for which the sponsor has **NO** reporting obligation of these cases in the EEA under the Directive 2001/20/EC.

When the sponsor does have clinical trials ongoing in the EEA with the same IMP, the reports of SUSARs from third country trials not authorised in the EEA should be submitted to EVCTM in accordance with the Directive 2001/20/EC. The 7 days reporting requirements for fatal and life threatening SUSARs apply. The recommendations detailed in point b) above should be followed.

It is important to maintain the structure of the concatenation with the '#' symbol ('YYYY-NNNNNN-CC#Study abbreviated name' or '#Study abbreviated name') in the data element *studyname* (ICH E2B(R2) A.2.3.1) to obtain a successful outcome of the validation of this data element. Failure of the validation on the first part of the reported data ('YYYY-NNNNNN-CC#' or '#') will generate an error message. Any local clinical trial numbers (used to identify clinical trials at national levels) should be entered in the data elements *sendercomment* (ICH E2B(R2) B.5.4).

The data element *studyname* (ICH E2B(R2) A.2.3.1) is limited to 100 characters. If necessary the study name should be abbreviated in the concatenation. The entire study name can be included in the data element *narrativeincludeclinical* (ICH E2B(R2) B.5.1).

8. ***drugrecurrence section and drugrecuraction***

The section *drugrecurrence* (E2B(R2) B.4.k.17.2) is not mandatory. The data element *drugrecuraction* (E2B(R2) B.4.k.17.2b) becomes mandatory if the section *drugrecurrence* is specified.

9. **Date Format Codes**

102 = CCYYMMDD	*(example: 12 JANUARY 1997 14:02:17 --> 19970112)*
203 = CCYYMMDDHHMM	*(example: 12 JANUARY 1997 14:02:17 --> 199701121402)*
204 = CCYYMMDDHHMMSS	*(example: 12 JANUARY 1997 14:02:17 --> 19970112140217)*
610 = CCYYMM	*(example: 12 JANUARY 1997 14:02:17 --> 199701)*
602 = CCYY	*(example: 12 JANUARY 1997 14:02:17 --> 1997)*

10. **Dates**

- Dates should be valid. They should conform to the corresponding date format (See note 9) and no date/time value should exceed the current UK GMT time plus 12 hours. Failure of the validation of the date format generates an error.
- All dates~~, except the values in the data elements *messagedate* (ICH M2 M.1.7b) and *transmissiondate* (ICH E2B(R2) A.1.3b),~~ should be inferior or equal to the ~~value in the data element *receiptdate* (ICH E2B(R2) A.1.7b)~~ EudraVigilance Gateway date. Failure of this validation generates an error.
- Each start date entered in the data elements *patientmedicalstartdate* (ICH E2B(R2) B.1.7.1c), *patientdrugstartdate* (ICH E2B(R2) B.1.8c), *parentmedicalstartdate* (ICH E2B(R2) B.1.10.7.1c), *parentdrugstartdate* (ICH E2B(R2) B.1.10.8c), *reactionstartdate* (ICH E2B(R2) B.2.i.4b) and *drugstartdate* (ICH E2B(R2) B.1.8c) should be inferior or equal to the specified end date. Failure of this validation generates an error.
- Each end date entered in the data elements *patientmedicalenddate* (ICH E2B(R2) B.1.7.1f), *patientdrugenddate* (ICH E2B(R2) B.1.8e), *parentmedicalenddate* (ICH E2B(R2) B.1.10.7.1f), *parentdrugenddate* (ICH E2B(R2) B.1.10.8e), *reactionenddate* (ICH E2B(R2) B.2.i.5b), *drugenddate* (ICH E2B(R2) B.4.k.14b) should be superior or equal to the specified start date. Failure of this validation generates an error.

11. **EVCT-ICSR**

Primarysource (ICH E2B(R2) A.2) iterations are repeatable sections. Therefore the data elements *studyname* (ICH E2B(R2) A.2.3.1), *sponsorstudynumb* (ICH E2B(R2) A.2.3.2) and *observestudytype* (ICH E2B(R2) A.2.3.3) need to be specified in at least one section for each EVCT-ICSR.

The EVCT-ICSR will only be accepted by EVCTM if these data elements are reported in at least one primary source section. If provided in more than one primary source section, the information in these data elements should be the same between each primary source section. Failure to this validation will generate an error report.

12. ***medicinalproduct* and *activesubstancename***

The presence of at least one of the data elements *medicinalproduct* (ICH E2B(R2) B.4.k.2.1) or *activesubstancename* (ICH E2B(R2) B.4.k.2.2) is mandatory. In each drug section, at least one of these data elements should be populated otherwise the validation performed by EV generates an error.

For combination products, the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) needs to be repeated for each active substance as necessary.

Where medicinal products cannot be described on the basis of the active substance(s) or the invented name, e.g. in case only the therapeutic class is reported by the primary source, or in case of other administered therapies that cannot be structured, this information should be reflected in the data element *narrativeincludeclinical* (ICH E2B(R2) B.5.1).

For cases submitted to EVCTM, the population of the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) is mandatory when the value in the data element *drugcharacterisation* (ICH E2B(R2) B.4.k.1) is '1' (suspect) or '3' (interacting). Failure of this validation generates an error.

For cases submitted to EVCTM, for which it is not possible to recode against EVMPD active substance names or codes provided in the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) and characterised as suspect or interacting, line listings of those cases will be sent regularly to sponsors of interventional clinical trials. Action to populate EVMPD with investigational medicinal products

information not already included and to resubmit the corrected cases should take place immediately and no later than 15 days following the receipt of the listings.

13. ***sendertelextension, senderfaxextension, receivertelextension, receiverfaxextension***

If the length is greater than 5 characters the system generates a warning, otherwise if it is greater than 10 characters the system generates an error.

14. ***messagereceiveridentifier***

When submitting a Safety Message to EV, the value accepted in the data element *messagereceiveridentifier* (ICH M2 M.1.5) is one of the following, depending to which module the message is addressed:

- 'EVTEST' (Test environment – EVPM)
- 'EVHUMAN' (Production environment – EVPM)
- 'EVCTMTEST' (Test environment – EVCTM)
- 'EVCTMPROD' (Production environment – EVCTM).

15. **Lookups on test name**

The ICSRs including tests should report in the data element *testname* (ICH E2B(R2) B.3.1c) a valid MedDRA LLT name or code. The failure of a successful match with the MedDRA lookup generates an error. If necessary, test names and results can be provided in free text in the data element *resultstestsprocedures* (ICH E2B(R2) B.3.2).

16. ***messagetype***

When submitting a Safety Message to EV, the value accepted in the data element *messagetype* (ICH M2 M.1.1) is one of the following:

- 'ichicsr' for expedited ICSRs submitted to EVPM or EVCTM;
- 'backlog' for retrospective ICSRs submitted to EVPM. This allows the exclusion of these reports from expedited reporting compliance checks. Separate business rules apply for the retrospective population of EVPM. They are described in Part III of Volume 9A of the Rules Governing Medicinal Products in the European Union;
- 'backlogct' for retrospective ICSRs submitted to EVCTM. This allows the exclusion of these reports from expedited reporting compliance checks;
- 'psur' for the periodic transmission of ICSRs not transmitted on an expedited basis in electronic format to EVPM;
- 'ctasr' for the periodic transmission of ICSRs not transmitted on an expedited basis in electronic format to EVCTM.

The value in the data element *messagetype* (ICH M2 M.1.1) is case-sensitive and should be reported in lower case.

17. ***casenullification***

No follow-up report can be submitted for cases which have been previously nullified. When an ICSR contains the value '1' (yes) in the data element *casenullification* (ICH E2B(R2) A.1.13), an error message will be generated for any additional follow-up report submitted for this case. A new case with a different 'Worldwide unique case identification number' (data element *authoritynumb* (ICH E2B(R2) A.1.10.1) or *companynumb* (ICH E2B(R2) A.1.10.2)) should be created and submitted if necessary.

18. ***Serious and seriousness***

The population of the data elements *serious* (ICH E2B(R2) A.1.5.1) is mandatory.

~~The population of the data elements *seriousness* (ICH E2B(R2) A.1.5.2) is mandatory when the value in the data element *serious* (ICH E2B(R2) A.1.5.1) is '1' (yes).~~

At least one of the data elements *seriousness* (ICH E2B(R2) A.1.5.2) should be populated with the value '1' (yes) when the data elements *serious* (ICH E2B(R2) A.1.5.1) is populated with the value '1' (yes). The remaining fields of the data elements *seriousness* (ICH E2B(R2) A.1.5.2) can have the values '1' (yes), '2' (no) or be left empty.

If one of the data elements *seriousness* (ICH E2B(R2) A.1.5.2) contains the value '1' (yes), the data element *serious* (ICH E2B(R2) A.1.5.1) should be populated with the value '1' (yes).

Failure to these validations will generate an error message.

19. **Qualification of the Primary Source**

At least one primary source included in the repeatable section *primarysource* (ICH E2B(R2) A.2) should have information regarding the qualification of the primary source reported in the data elements *qualification* (ICH E2B(R2) A.2.1.4) with one of the following numerical values: '1' (physician), '2' (pharmacist), '3' (other health professional), '4' (lawyer) or '5' (consumer or a non-health professional).

Failure to comply with this validation will generate an error report. This is a temporary measure to be applied for a 12-month period from the date of publication of this guidance, in order to allow stakeholders the possibility to update their system. Following this transitional period any primary source included in the repeatable section *primarysource* (ICH E2B(R2) A.2) should have a qualification reported in the data elements *qualification* (ICH E2B(R2) A.2.1.4).

20. **Section *drugreactionrelatedness* (ICH E2B (R2) B.4.k.18)**

This section provides the means to transmit the degree of suspected relatedness of each reported medicinal product to each reported event/reaction.

The repeatable subsections should be used to submit the assessment of the causality of each reported medicinal product classified as suspect or interacting for each reported event/reaction.

The repeatable subsections allow for the assessment to be provided for different sources of information. They also give the option to apply other methods of causality assessment in addition to the mandatory binary decision method described in Note 23.

21. **Data element *drugreactionasses* (ICH E2B (R2) B.4.k.18.1)**

Each individual event/reaction reported in the ICSR should have a causality assessment assigned for each reported medicinal product classified as suspect or interacting. This section should contain all the same MedDRA LLT code(s) as the one(s) reported in the data element *reactionmeddrallt* (ICH E2B(R2) B.2.i.1.b). The reported MedDRA version should be identical as the one detailed in the data element *reactionmeddraversionllt* (ICH E2B(R2) B.2.i.2.a).

22. **Data element *drugassessmentsource* (ICH E2B (R2) B.4.k.18.2)**

This data element allows to the identification of the source of assessment (Investigator, Sponsor, NCA) of the causality provided for each event/reaction reported in ICSRs.

A controlled vocabulary has been introduced in order to avoid error reporting. Only numerical values, as presented in Table 5, are accepted in the data element *drugassessmentsource* (ICH E2B (R2) B.4.k.18.2) when the value in the data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) is 'EVCTM'.

Table 5. Accepted values in the data element *drugassessmentsource* (ICH E2B (R2) B.4.k.18.2) when the value in the data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) is 'EVCTM'

SOURCE OF ASSESSMENT (ICH E2B (R2) B.4.k.18.2)	VALUE
Investigator	1
Sponsor	2
NCA	3

23. **Data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3)**

Numerous methods of causality assessment of adverse drug reactions have been published in the literature and are currently used worldwide[12]. Based on this principle, ICH E2B(R2) allows the possibility to provide several results of causality assessment by using one or more methods of assessment.

At least one method of assessment corresponding to the binary decision method detailed in the CIOMS Working Group VI report[13] should be provided for each reported adverse event/reaction. The binary decision method ('Reasonable possibility' or 'No reasonable possibility'), should be used to report the causal association between each reported medicinal product classified as suspect or interacting and each reported event/reaction. This method of assessment should be characterised with the value 'EVCTM' in the data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3). The use of other methods of causality assessment is optional. Table 7 provides examples on how to populate this data element.

24. **Data element *drugresult* (ICH E2B (R2) B.4.k.18.4)**

This data element is used to submit the result of the causality assessment of each medicinal product classified as suspect or interacting for each event/reaction reported in the ICSR.

A controlled vocabulary has been introduced in order to avoid error reporting when providing a causality assessment result in accordance with the binary decision method described in Note 23. Only numerical values, as presented in Table 6, are accepted in the data element *drugresult* (ICH E2B (R2) B.4.k.18.4) when the value in the data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) is 'EVCTM'.

When using other methods of causality assessment, the sponsor should decide which categories of causality assessment result correspond to 'Reasonable possibility' and which ones refer to 'No reasonable possibility'.

[12] Methods of causality assessment of adverse drug reaction. A systematic review; Agbabiak T.B., Savovic J., Ernst E. Drug Safety 2008: 31(1): 21-37.
[13] Management of Safety Information from Clinical Trials CIOMS Working Group VI (CIOMS, Geneva 2005).

Table 6. Accepted values in the data element *drugresult* (ICH E2B (R2) B.4.k.18.4) when the value in the data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) is 'EVCTM'

RESULT OF ASSESSMENT (ICH E2B (R2) B.4.k.18.4)	VALUE
Reasonable possibility	1
No reasonable possibility	2

Each MedDRA LLT code reported in the data element *reactionmeddrallt* (ICH E2B(R2) B.2.i.1.b) should have an assessment provided by the Investigator AND/OR by the Sponsor for each reported medicinal product classified as suspect or interacting. Failure to comply with this requirement generates an error report.

Any initial ICSR should contain at least one reaction with a causality assessment 'Reasonable possibility' (based on the binary decision method detailed in the CIOMS Working Group VI report) to at least one of the reported medicinal products classified as suspect or interacting. If this information is not available, the ICSR submitted to EVCTM is classified as an error report and requires correction and resubmission if applicable. This rule is not applied to follow-up ICSRs submitted to EVCTM in order to allow to sponsors the possibility to downgrade the causality of an initial ICSR.

Examples on how to provide information on causality assessment are provided in Table 7.

When the sponsor is sending the report at an early stage and does not have sufficient information to assign causalities between the reported medicinal products classified as suspect or interacting and the reported adverse events/reactions, a 'Reasonable possibility' of causal association should be considered until further information is available to confirm or downgrade the initially reported causality.

Table 7. Examples of reporting of causality assessment of 2 medicinal products (Medicinal Product A and Medicinal Product B) considered suspect or interacting for 3 events (Event 1, Event 2 and Event 3)

REACTION ASSESSED (ICH E2B (R2) B.4.k.18.1b)	SOURCE OF ASSESSMENT (ICH E2B (R2) B.4.k.18.2) [a]	METHOD OF ASSESSMENT (ICH E2B (R2) B.4.k.18.3) [b]	RESULT OF ASSESSMENT (ICH E2B (R2) B.4.k.18.4) [c]	INFORMATION TO BE REPORTED TO EVCTM [b]
k(1) = Medicinal Product A (considered suspect or interacting) [d]				
Event 1 LLT MedDRA code	Investigator	Expert judgment	Definite	Optional
Event 1 LLT MedDRA code	Sponsor	Algorithm	Probable	Optional
Event 1 LLT MedDRA code	**2**	**EVCTM**	**1**	**Mandatory**
Event 2 LLT MedDRA code	Investigator	Expert judgment	Doubtful	Optional
Event 2 LLT MedDRA code	Sponsor	Algorithm	Possible	Optional
Event 2 LLT MedDRA code	**2**	**EVCTM**	**1**	**Mandatory**
Event 3 LLT MedDRA code	Investigator	Expert judgment	Unrelated	Optional

REACTION ASSESSED (ICH E2B (R2) B.4.k.18.1b)	SOURCE OF ASSESSMENT (ICH E2B (R2) B.4.k.18.2) [a]	METHOD OF ASSESSMENT (ICH E2B (R2) B.4.k.18.3) [b]	RESULT OF ASSESSMENT (ICH E2B (R2) B.4.k.18.4) [c]	INFORMATION TO BE REPORTED TO EVCTM [b]
Event 3 LLT MedDRA code	Sponsor	Algorithm	Excluded	Optional
Event 3 LLT MedDRA code	**2**	**EVCTM**	**2**	**Mandatory**
k(2) = Medicinal Product B (considered suspect or interacting) [d]				
Event 1 LLT MedDRA code	Sponsor	Algorithm	No reasonable possibility	Optional
Event 1 LLT MedDRA code	**2**	**EVCTM**	**2**	**Mandatory**
Event 2 LLT MedDRA code	Investigator	Expert judgment	Unrelated	Optional
Event 2 LLT MedDRA code	NCA	Algorithm	Possible	Optional
Event 2 LLT MedDRA code	Sponsor	Algorithm	Reasonable possibility	Optional
Event 2 LLT MedDRA code	**2**	**EVCTM**	**1**	**Mandatory**
Event 3 LLT MedDRA code	Investigator	Expert judgment	Definite	Optional
Event 3 LLT MedDRA code	**1**	**EVCTM**	**1**	**Mandatory**

[a] Each reported adverse event/reaction should have at least one causality assessment provided by the Investigator AND/OR by the Sponsor for each reported medicinal product classified as suspect or interacting. The accepted value in the Data element *drugassessmentsource* (ICH E2B (R2) B.4.k.18.2) is '1', '2' or '3' when the value in the Data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) is 'EVCTM'.

[b] At least one method of assessment corresponding to the binary decision method described in Note 23 should be provided for each reported adverse event/reaction. This method should be reported in the data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) with the value 'EVCTM'. Provision in free text of other methods of causality assessment is optional.

[c] The accepted value in the Data element *drugresult* (ICH E2B (R2) B.4.k.18.4) is '1' or '2' when the value in the Data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) is 'EVCTM'. Provision in free text of results of assessment based on other methods of causality is optional.

[d] The order of the rows is not important since each one represents a complete set of information, however all assessments for the Medicinal Product A (k=1) classified as suspect or interacting should appear before the assessments for the Medicinal Product B (k=2) classified as suspect or interacting.

25. **Data element *reporterstate* (ICH E2B (R2) A.2.1.2e) and *reporterpostcode* (ICH E2B (R2) A.2.1.2f)**

For cases originating in SPAIN, at least one of the data elements *reporterstate* (ICH E2B (R2) A.2.1.2e) or *reporterpostcode* (ICH E2B (R2) A.2.1.2f) should be populated in accordance with the requirements presented in Appendix H.

26. **Numeric codes for units and intervals**

CODES	UNITS & INTERVALS LIST	CODES	UNITS & INTERVALS LIST
001	kg kilogram(s)	023	Mmol millimole(s)
002	G gram(s)	024	µmol micromole(s)
003	Mg milligram(s)	025	Iu international unit(s)
004	µg microgram(s)	026	Kiu iu(1000s)
005	ng nanogram(s)	027	Miu iu(1,000,000s)
006	pg picogram(s)	028	iu/kg iu/kilogram
007	mg/kg milligram(s)/kilogram	029	Meq milliequivalent(s)
008	µg/kg microgram(s)/kilogram	030	% percent
009	mg/m2 milligram(s)/sq. meter	031	Gtt drop(s)
010	µg/ m2 microgram(s)/ sq. meter	032	Kbq kilobecquerel(s)
011	l litre(s)	800	Decade(s)
012	ml millilitre(s)	801	Year(s)
013	µl microlitre(s)	802	Month(s)
014	Bq becquerel(s)	803	Week(s)
015	GBq gigabecquerel(s)	804	Day(s)
016	MBq megabecquerel(s)	805	Hour(s)
017	Kbq kilobecquerel(s)	806	Minute(s)
018	Ci curie(s)	807	Second(s)
019	MCi millicurie(s)	810	Trimester(s)
020	µCi microcurie(s)	811	Cyclical
021	NCi nanocurie(s)	812	As Necessary
022	Mol mole(s)	813	Total

Appendix B: Business Rules applicable to EVPM and EVCTM (Warning Generation)

Table Legend: See Appendix A (Table Legend)

This chapter summarises the list of the business rules (Table 8) generating warning messages by EV in case of non compliance.

Table 8. List of all business rules generating warning messages

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
A.3.1.4g	sendertelextension	10	AN			See note 1 (warning/error)
A.3.1.4j	senderfaxextension	10	AN			See note 1 (warning/error)
A.3.2.3g	receivertelextension	10	AN			See note 1 (warning/error)
A.3.2.3j	receiverfaxextension	10	AN			See note 1 (warning/error)
B.1.8a	patientdrugname	100	AN	Lookup on Medicinal Products (warning)		See note 2
B.1.10.8a	parentdrugname	100	AN	Lookup on Medicinal Products (warning)		See note 2
B.3.1e	testunit	35	AN		Mandatory (warning) if B.3.1d is not NULL	
B.4.k.2.1	medicinalproduct	70	AN	Lookup on Medicinal Products (warning)		At least one of B.4.k.2.1- B.4.k.2.2 (error). See note 2
B.4.k.2.2	activesubstancename	100	AN	Lookup on Substances (warning)	Mandatory for any transmission to EVCTM (error) or EVPM (warning) when the value in B.4.k.1 is (1) or (3)	At least one of B.4.k.2.1- B.4.k.2.2 (error). See note 2
B.4.k.7	drugdosageform	100	AN	Lookup on Dosage forms (warning)		See note 3

B.1 Notes:

1. ***sendertelextension, senderfaxextension, receivertelextension, receiverfaxextension***

If the length is greater than 5 characters the system generates a warning, otherwise if it is greater than 10 characters the system generates an error.

2. ***medicinalproduct and activesubstancename***

The presence of at least one of the data elements *medicinalproduct* (ICH E2B(R2) B.4.k.2.1) or *activesubstancename* (ICH E2B(R2) B.4.k.2.2) is mandatory. In each drug section at least one of these data elements should appear, otherwise the validation performed by EV generates an error.

For combination products, the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) needs to be repeated for each active substance as necessary.

Where medicinal products cannot be described on the basis of the active substance(s) or the invented name, e.g. in case only the therapeutic class is reported by the primary source, or in case of other administered therapies that cannot be structured, this information should be reflected in the data element *narrativeincludeclinical* (ICH E2B(R2) B.5.1).

Warning refers only to the following validations:

- The failure of a successful match of data elements *medicinalproduct* (ICH E2B(R2) B.4.k.2.1), *patientdrugname* (ICH E2B(R2) B.1.8.a) and *parentdrugname* (ICH E2B(R2) B.1.10.8.a) with the EVMPD lookup on medicinal products generates a warning;
- The failure of a successful match of data elements *activvesubstancename* (ICH E2B(R2) B.4.k.2.2) with the EVMPD lookup on active substances generates a warning. However, for cases submitted to EVCTM, for which it is not possible to recode against EVMPD active substance names or codes provided in the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) and characterised as suspect or interacting, line listings of those cases will be sent regularly to sponsors of interventional clinical trials. Action to populate EVMPD with investigational medicinal products information not already included and to resubmit the corrected cases should take place immediately and no later than 15 days following the receipt of the listings;
- For cases submitted to EVPM, the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) should be populated when the value in the data element *drugcharacterisation* (ICH E2B(R2) B.4.k.1) is '1' (suspect) or '3' (interacting). Failure of this validation generates a warning.

3. ***drugdosageform***

If data element *drugdosageform* (ICH E2B(R2) B.4.k.7) is not null, the failure of a successful match with the latest version of the European Pharmacopoeia Dosage Forms list generates a warning.

See http://eudravigilance.emea.europa.eu/human/PharmaceuticalDoseFormsUpdate.asp (or http://eudravigilance.ema.europa.eu/human/PharmaceuticalDoseFormsUpdate.asp) for the version currently implemented in EudraVigilance. If the drug dosage form is not available in the latest version of the European Pharmacopoeia Dosage Forms list or is under proposal, the information should only be entered in the data element *narrativeincludeclinical* (ICH E2B(R2) B.5.1).

Appendix C: Business Rules (Complete list)

This chapter describes the complete set of validation processes performed by EV.

Table Legend: See Appendix A (Table Legend)

C.1 Rules applicable to EVPM and/or EVCTM

Table 9 summarises the complete list of the business rules applicable to EV. This is the list of all the rules, including those presented in Appendix A generating error messages and in Appendix B generating warning messages. For the list of rules applicable to EVPM exclusively or EVCTM exclusively refer to Section C.2 or C.3 respectively.

Table 9. List of all business rules applicable to EV

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
M.1	**ichicsrmessageheader**				**Mandatory**	
M.1.1	messagetype	16	AN	(ichicsr, backlog, backlogct, psur, ctasr)	Mandatory	See note 19
M.1.2	messageformatversion	3	AN	(2.1)	Mandatory	
M.1.3	messageformatrelease	3	AN	(1, 1.0, 2, 2.0)	Mandatory	
M.1.4	messagenumb	100	AN		Mandatory	
M.1.5	messagesenderidentifier	60	AN		Mandatory	
M.1.6	messagereceiveridentifier	60	AN		Mandatory	See note 18
M.1.7a	messagedateformat	3	N	(204)	Mandatory	See note 1
M.1.7b	messagedate	14	N	Date	Mandatory	Should conform to M.1.7a. See note 15
A.1	**safetyreport**				**Mandatory**	**(1...∞)**
	safetyreportversion	2	AN			
A.1.0.1	safetyreportid	100	AN	(valid ISO3166 country code-regulator or company name-report number)	Mandatory	
A.1.1	primarysourcecountry	2	A	Lookup on ISO3166	Mandatory	See note 16
A.1.2	occurcountry	2	A	Lookup on ISO3166		See note 16
A.1.3a	transmissiondateformat	3	N	(102)	Mandatory	See note 1
A.1.3b	transmissiondate	8	N	Date	Mandatory	Should conform to A.1.3a. See note 15
A.1.4	Reporttype	1	N	[1-4] 1=Spontaneous 2=Report from study 3=Other 4=Not available to sender (unknown)	Mandatory	See note 8
A.1.5.1	Serious	1	N	(1,2) 1=Yes 2=No	Mandatory. See note 21	Accepted value is (1) if one of A.1.5.2 values is (1)
A.1.5.2	seriousnessdeath	1	N	(1,2) 1=Yes 2=No	If A.1.5.1 value is (1), at least one of the	See note 9
	seriousnesslifethreate	1	N	(1,2)		

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
	ning			1=Yes 2=No	values should be (1). See note 21	
	seriousnesshospitalization	1	N	(1,2) 1=Yes 2=No		
	seriousnessdisabling	1	N	(1,2) 1=Yes 2=No		
	Seriousnesscongenitalanomali	1	N	(1,2) 1=Yes 2=No		
	seriousnessother	1	N	(1,2) 1=Yes 2=No		
A.1.6a	receivedateformat	3	N	(102)	Mandatory	See note 1
A.1.6b	receivedate	8	N	Date	Mandatory	Should be ≤ to A.1.7b and should conform to A.1.6a. See note 15
A.1.7a	receiptdateformat	3	N	(102)	Mandatory	See note 1
A.1.7b	receiptdate	8	N	Date	Mandatory	Should be ≥ to A.1.6b and should conform to A.1.7a. See note 15
A.1.8.1	additionaldocument	1	N	(1,2) 1=Yes 2=No		
A.1.8.2	documentlist	100	AN			
A.1.9	fulfillexpeditecriteria	1	N	(1,2) 1=Yes 2=No		
A.1.10.1	authoritynumb	100	AN	(valid ISO3166 country code-regulator name-report number)	Mandatory	One of A.1.10.1 or A.1.10.2 accepted See note 3
A.1.10.2	companynumb	100	AN	(valid ISO3166 country code-company name-report number)	Mandatory	One of A.1.10.1 or A.1.10.2 accepted See note 3
	reportduplicate					
A.1.11	duplicate	1	N	(1) 1=Yes		
A.1.11.1	duplicatesource	50	AN			
A.1.11.2	duplicatenumb	100	AN			
A.1.12	linkreportnumb	100	AN			
A.1.13	casenullification	1	N	(1) 1=Yes		See note 20
A.1.13.1	nullificationreason	200	AN			
A.1.14	Medicallyconfirm	1	N	(1,2) 1=Yes 2=No		See note 10
A.2	**primarysource**				**Mandatory**	**(1…∞)**
A.2.1.1a	reportertitle	50	AN			
A.2.1.1b	reportergivename	35	AN			
A.2.1.1c	reportermiddlename	15	AN			
A.2.1.1d	reporterfamilyname	50	AN			At least one of A.2.1.1d, A.2.1.2a, A.2.1.2f, A.2.1.3, A.2.2, A.2.3.1
A.2.1.2a	reporterorganization	60	AN			At least one of A.2.1.1d, A.2.1.2a, A.2.1.2f, A.2.1.3, A.2.2, A.2.3.1
A.2.1.2b	reporterdepartment	60	AN			
A.2.1.2c	reporterstreet	100	AN			
A.2.1.2d	reportercity	35	AN			
A.2.1.2e	reporterstate	40	AN		Mandatory for cases originating in Spain (one of A.2.1.2e or A.2.1.2f)	See note 27
A.2.1.2f	reporterpostcode	15	AN		Mandatory for cases	At least one of A.2.1.1d, A.2.1.2a,

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
					originating in Spain (one of A.2.1.2e or A.2.1.2f)	A.2.1.2f, A.2.1.3, A.2.2, A.2.3.1 See note 27
A.2.1.3	reportercountry	2	A	Lookup on ISO3166		At least one of A.2.1.1d, A.2.1.2a, A.2.1.2f, A.2.1.3, A.2.2, A.2.3.1
A.2.1.4	qualification	1	N	[1-5] 2=Pharmacist 3=Other Health Professional 4=Lawyer 5=Consumer or other non health professional	Mandatory	See note 10
A.2.2	literaturereference	500	AN			At least one of A.2.1.1d, A.2.1.2a, A.2.1.2f, A.2.1.3, A.2.2, A.2.3.1
A.2.3.1	studyname	100	AN		Mandatory for any transmission to EVCTM.	At least one of A.2.1.1d, A.2.1.2a, A.2.1.2f, A.2.1.3, A.2.2, A.2.3.1. See note 13 and 17
A.2.3.2	sponsorstudynumb	35	AN		Mandatory for any transmission to EVCTM.	See note 17
A.2.3.3	observestudytype	1	N	(1,2,3) 1=Clinical trials 2=Individual patient use 3=Other studies	Mandatory if A.1.4 value is (2).	See note 8 and 17
A.3.1	**sender**				**Mandatory**	
A.3.1.1	sendertype	1	N	[1-6] 1=Pharmaceutical Company 2=Regulatory Authority 3=Health professional 4=Regional Pharmacovigilance Center 5=WHO Collaborating Center for International Drug Monitoring 6=Other		
A.3.1.2	senderorganization	60	AN		Mandatory	
A.3.1.3a	senderdepartment	60	AN			
A.3.1.3b	sendertitle	10	AN			
A.3.1.3c	sendergivename	35	AN			
A.3.1.3d	sendermiddlename	15	AN			
A.3.1.3e	senderfamilyname	35	AN			
A.3.1.4a	senderstreetaddress	100	AN			
A.3.1.4b	sendercity	35	AN			
A.3.1.4c	senderstate	40	AN			
A.3.1.4d	senderpostcode	15	AN			
A.3.1.4e	sendercountrycode	2	A	Lookup on ISO3166		
A.3.1.4f	sendertel	10	AN			
A.3.1.4g	sendertelextension	10	AN			See note 5 (warning/error)
A.3.1.4h	sendertelcountrycode	3	AN			
A.3.1.4i	senderfax	10	AN			
A.3.1.4j	senderfaxextension	10	AN			See note 5

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
						(warning/error)
A.3.1.4k	senderfaxcountrycode	3	AN			
A.3.1.4l	senderemailaddress	100	AN			
A.3.2	**receiver**				**Mandatory**	
A.3.2.1	receivertype	1	N	(1,2,4,5,6) 1=Pharmaceutical Company 2=Regulatory Authority 4=Regional Pharmacovigilance Center 5=WHO Collaborating Center for International Drug Monitoring 6=Other		
A.3.2.2a	receiverorganization	60	AN		Mandatory	
A.3.2.2b	receiverdepartment	60	AN			
A.3.2.2c	receivertitle	10	AN			
A.3.2.2d	receivergivename	35	AN			
A.3.2.2e	receivermiddlename	15	AN			
A.3.2.2f	receiverfamilyname	35	AN			
A.3.2.3a	receiverstreetaddress	100	AN			
A.3.2.3b	receivercity	35	AN			
A.3.2.3c	receiverstate	40	AN			
A.3.2.3d	receiverpostcode	15	AN			
A.3.2.3e	receivercountrycode	2	A	Lookup on ISO3166		
A.3.2.3f	receivertel	10	AN			
A.3.2.3g	receivertelextension	10	AN			See note 5 (warning/error)
A.3.2.3h	receivertelcountrycode	3	AN			
A.3.2.3i	receiverfax	10	AN			
A.3.2.3j	receiverfaxextension	10	AN			See note 5 (warning/error)
A.3.2.3k	receiverfaxcountrycode	3	AN			
A.3.2.3l	receiveremailaddress	100	AN			
B.1	**patient**				**Mandatory**	
B.1.1	patientinitial	10	AN			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5
B.1.1.1a	patientgpmedicalrecordnumb	20	AN			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5
B.1.1.1b	patientspecialistrecordnumb	20	AN			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5
B.1.1.1c	patienthospitalrecordnumb	20	AN			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a -

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
						B.1.2.3 – B.1.5
B.1.1.1d	patientinvestigationnumb	20	AN			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5
B.1.2.1a	patientbirthdateformat	3	N	(102)	Mandatory if B.1.2.1b is not NULL	See note 1
B.1.2.1b	patientbirthdate	8	N	Date		At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5. Should conform to B.1.2.1a. See note 15
B.1.2.2a	patientonsetage	5	N			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5. If not NULL, should not be > 150 years. See note 11
B.1.2.2b	patientonsetageunit	3	N	[800-805]	Mandatory if B.1.2.2a is not NULL	See note 28
B.1.2.2.1a	gestationperiod	3	N			At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5
B.1.2.2.1b	gestationperiodunit	3	N	(802,803,804,810)	Mandatory if B.1.2.2.1a is not NULL	See note 28
B.1.2.3	patientagegroup	1	N	[1-6] 1=Neonate 2=Infant 3=Child 4=Adolescent 5=Adult 6=Elderly		At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5
B.1.3	patientweight	6	N			If not null, should not be > 650 kg. See note 11
B.1.4	patientheight	3	N			If not null, should not be > 250 cm. See note 11
B.1.5	patientsex	1	N	(1,2) 1=Male 2=Female		At least one of B.1.1- B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - B.1.2.1b -B.1.2.2a - B.1.2.2.1a - B.1.2.3 – B.1.5
B.1.6a	lastmenstrualdateformat	3	N	(102,610,602)	Mandatory if B.1.6b not NULL	Should be NULL if B.1.5 value is (1) (patient is male).

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
						See note 1
B.1.6b	patientlastmenstrualdate	8	N	Date		Should conform to B.1.6a. Should be NULL if B.1.5 value is (1) (patient is male). See note 15
B.1.7	**medicalhistoryepisode**					**(0...∞)**
B.1.7.1a.1	patientepisodenamemeddraversion	8	AN	x.x	Mandatory if B.1.7.1a.2 is not NULL	See note 4
B.1.7.1a.2	patientepisodename	250	N	Lookup on MedDRA LLT		See note 4
B.1.7.1b	patientmedicalstartdateformat	3	N	(102,610,602)	Mandatory if B.1.7.1c not NULL	See note 1
B.1.7.1c	patientmedicalstartdate	8	N	Date		Should precede B.1.7.1f and conform to B.1.7.1b. See note 15
B.1.7.1d	patientmedicalcontinue	1	N	(1,2,3) 1=Yes 2=No 3=Unknown		
B.1.7.1e	patientmedicalenddateformat	3	N	(102,610,602)	Mandatory if B.1.7.1f not NULL	See note 1
B.1.7.1f	patientmedicalenddate	8	N	Date		Should follow B.1.7.1c and conform to B.1.7.1e. See note 15
B.1.7.1g	patientmedicalcomment	100	AN			
B.1.7.2	patientmedicalhistorytext	10000	AN			
B.1.8	**patientpastdrugtherapy**					**(0...∞)**
B.1.8a	patientdrugname	100	AN	Lookup on Medicinal Products (warning)		See note 2
B.1.8b	patientdrugstartdateformat	3	N	(102,610,602)	Mandatoy if B.1.8c not NULL	See note 1
B.1.8c	patientdrugstartdate	8	N	Date		Should precede B.1.8e and conform to B.1.8b. See note 15
B.1.8d	patientdrugenddateformat	3	N	(102,610,602)	Mandatory if B.1.8e not NULL	See note 1
B.1.8e	patientdrugenddate	8	N	Date		Should follow B.1.8c and conform to B.1.8d. See note 15
B.1.8f.1	patientindicationmeddraversion	8	AN	x.x	Mandatory if B.1.8f.2 is not NULL	See note 4
B.1.8f.2	patientdrugindication	250	N	Lookup on MedDRA LLT		See note 4
B.1.8g.1	patientdrugreactionmeddraversion	8	AN	x.x	Mandatory if B.1.8g.2 is not NULL	See note 4
B.1.8g.2	patientdrugreaction	250	N	Lookup on MedDRA LLT		See note 4
B.1.9	**patientdeath**					

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
B.1.9.1a	patientdeathdateformat	3	N	(102,610,602)	Mandatory if B.1.9.1b not NULL	See note 1
B.1.9.1b	patientdeathdate	8	N	Date		Should conform to B.1.9.1a. See note 15
B.1.9.2	**patientdeathcause**					**(0...∞)**
B.1.9.2a	patientdeathreportmeddraversion	8	AN	x.x	Mandatory if B.1.9.2.b is not NULL.	See note 4
B.1.9.2.b	patientdeathreport	250	N	Lookup on MedDRA LLT		See note 4
B.1.9.3	patientautopsyyesno	1	N	(1,2,3) 1=Yes 2=No 3=Unknown		
B.1.9.4	**patientautopsy**					**(0...∞)**
B.1.9.4a	patientdetermautopsmeddraversion	8	AN	x.x	Mandatory if B.1.9.4b is not NULL	See note 4
B.1.9.4b	patientdetermineautopsy	250	N	Lookup on MedDRA LLT		See note 4
B.1.10	**parent**					
B.1.10.1	parentidentification	10	AN			
B.1.10.2.1a	parentbirthdateformat	3	N	(102)	Mandatory if B.1.10.2.1b not NULL	See note 1
B.1.10.2.1b	parentbirthdate	8	N	Date		Should conform to B.1.10.2.1a. See note 15
B.1.10.2.2a	parentage	2	N			See note 11
B.1.10.2.2b	parentageunit	3	N	(801)	Mandatory if B.1.10.2.2a is not NULL	See note 28
B.1.10.3a	parentlastmenstrualdateformat	3	N	(102)	Mandatory if B.1.10.3b not NULL	Should be NULL if B.1.10.6 value is (1) (parent is male). See note1
B.1.10.3b	parentlastmenstrualdate	8	N	Date		Should conform to B.1.10.3a. Should be NULL if B.1.10.6 value is (1) (parent is male). See note 15
B.1.10.4	parentweight	6	N			If not null, should not be > 650 kg. See note 11
B.1.10.5	parentheight	3	N			If not null, should not be > 250 cm. See note11
B.1.10.6	parentsex	1	N	(1,2) 1=Male 2=Female		
B.1.10.7	**parentmedicalhistoryepisode**					**(0...∞)**
B.1.10.7.1a.1	parentmdepisodemeddraversion	8	AN	x.x	Mandatory if B.1.10.7.1a.2 is not NULL.	See note 4
B.1.10.7.1a.2	parentmedicalepisodename	250	N	Lookup on MedDRA LLT		See note 4
B.1.10.7.1b	parentmedicalstartdateformat	3	N	(102,610,602)	Mandatory if B.1.10.7.1c not NULL	See note 1
B.1.10.7.1c	parentmedicalstartdate	8	N	Date		Should precede B.1.10.7.1f and conform to B.1.10.7.1b. See

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
						note 15
B.1.10.7.1d	parentmedicalcontinue	1	N	(1,2,3) 1=Yes 2=No 3=Unknown		
B.1.10.7.1e	parentmedicalenddateformat	3	N	(102,610,602)	Mandatory if B.1.10.7.1f not NULL	See note 1
B.1.10.7.1f	parentmedicalenddate	8	N	Date		Should follow B.1.10.7.1c and conform to B.1.10.7.1e. See note 15
B.1.10.7.1g	parentmedicalcomment	100	AN			
B.1.10.7.2	parentmedicalrelevanttext	10000	AN			
B.1.10.8	**parentpastdrugtherapy**					**(0…∞)**
B.1.10.8a	parentdrugname	100	AN	Lookup on Medicinal Products (warning)		See note 2
B.1.10.8b	parentdrugstartdateformat	3	N	(102,610,602)	Mandatory if B.1.10.8c not NULL	See note 1
B.1.10.8c	parentdrugstartdate	8	N	Date		Should precede B.1.10.8e and conform to B.1.10.8b. See note 15
B.1.10.8d	parentdrugenddateformat	3	N	(102,610,602)	Mandatory if B.1.10.8e not NULL	See note 1
B.1.10.8e	parentdrugenddate	8	N	Date		Should follow B.1.10.8c and conform to B.1.10.8d. See note 15
B.1.10.8f.1	Parentdrugindicationmeddraversion	8	N	x.x	Mandatory if B.1.10.8f.2 is not NULL	See note 4
B.1.10.8f.2	parentdrugindication	250	N	Lookup on MedDRA LLT		See note 4
B.1.10.8g.1	parentdrugreactionmeddraversion	8	AN	x.x	Mandatory if B.1.10.8g.2 is not NULL	See note 4
B.1.10.8g.2	parentdrugreaction	250	N	Lookup on MedDRA LLT		See note 4
B.2	**reaction**				**Mandatory**	**(1…∞)**
B.2.i.1.0	primarysourcereaction	200	AN			
B.2.i.1.a	reactionmeddraversionllt	8	AN	x.x	Mandatory	See note 4
B.2.i.1.b	reactionmeddrallt	250	N	Lookup on MedDRA LLT	Mandatory	See note 4
B.2.i.2.a	reactionmeddraversionpt	8	AN	x.x	Mandatory if B.2.i.2.b is not NULL	See note 4
B.2.i.2.b	reactionmeddrapt	250	AN			See note 7
B.2.i.3	termhighlighted	1	N	(1,2,3,4) 1=Yes, highlighted by the reporter, NOT serious, 2=No, not highlighted by the reporter, NOT serious, 3=Yes, highlighted by the reporter,		

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
				SERIOUS, 4=No, not highlighted by the reporter, SERIOUS		
B.2.i.4a	reactionstartdateformat	3	N	(102,203,610,602)	Mandatory if B.2.i.4b not NULL	See note 1
B.2.i.4b	reactionstartdate	12	N	Date		Should precede B.2.i.5b and conform to B.2.i.4a. See note 15
B.2.i.5a	reactionenddateformat	3	N	(102,203,610,602)	Mandatory if B.2.i.5b not NULL	See note 1
B.2.i.5b	reactionenddate	12	N	Date		Should follow B.2.i.4b and conform to B.2.i.5a. See note 15
B.2.i.6a	reactionduration	5	N			
B.2.i.6b	reactiondurationunit	3	N	[801-807]	Mandatory if B.2.i.6a is not NULL	See note 28
B.2.i.7.1a	reactionfirsttime	5	N			
B.2.i.7.1b	reactionfirsttimeunit	3	N	[801-807]	Mandatory if B.2.i.7.1a is not NULL	See note 28
B.2.i.7.2a	reactionlasttime	5	N			
B.2.i.7.2b	reactionlasttimeunit	3	N	[801-807]	Mandatory if B.2.i.7.2a is not NULL	See note 28
B.2.i.8	reactionoutcome	1	N	[1-6] 1=recovered/ resolved 2=recovering/ resolving 3=not ecovered/ not resolved 4=recovered/ resolved with sequelae 5=fatal 6=unknown	Mandatory	At least one of B.2.i.8 should contain the value (5) if A.1.5.2 seriousnessdeath value is (1). See note 9
B.3	**test**					
B.3.1a	testdateformat	3	N	(102,610,602)	Mandatory if B.3.1b not NULL	See note 1
B.3.1b	testdate	8	N	Date		Should conform to B.3.1a. See note 15
B.3.1c	testname	100	N	Lookup on MedDRA LLT		See note 14
B.3.1d	testresult	50	AN			
B.3.1e	testunit	35	AN		Mandatory (warning) if B.3.1d is not NULL	
B.3.1.1	lowtestrange	50	AN			
B.3.1.2	hightestrange	50	AN			
B.3.1.3	moreinformation	1	N	(1,2) 1=Yes 2= No		
B.3.2	resultstestsprocedures	2000	AN			
B.4	**drug**				**Mandatory**	**(1...∞)**
B.4.k.1	drugcharacterization	1	N	(1,2,3) 1=Suspect 2=Concomitant 3=Interacting	Mandatory	At least one of B.4.k.1 values should be (1) or (3)
B.4.k.2.1	medicinalproduct	70	AN	Lookup on		At least one of

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
				Medicinal Products (warning)		B.4.k.2.1-B.4.k.2.2 (error). See note 2
B.4.k.2.2	activesubstancename	100	AN	Lookup on Substances (warning)	Mandatory for any transmission to EVCTM (error) or EVPM (warning) when the value in B.4.k.1 is (1) or (3)	At least one of B.4.k.2.1 and B.4.k.2.2 (error). See note 2
B.4.k.2.3	obtaindrugcountry	2	A	Lookup on ISO3166		
B.4.k.3	drugbatchnumb	35	AN			
B.4.k.4.1	drugauthorizationnumb	35	AN			
B.4.k.4.2	drugauthorizationcountry	2	A	Lookup on ISO3166		
B.4.k.4.3	drugauthorizationholder	60	AN			
B.4.k.5.1	drugstructuredosagenumb	8	N			
B.4.k.5.2	drugstructuredosageunit	3	N	[001-032]	Mandatory if B.4.k.5.1 is not NULL	See note 28
B.4.k.5.3	drugseparatedosagenumb	3	N			
B.4.k.5.4	drugintervaldosageunitnumb	3	N			
B.4.k.5.5	drugintervaldosagedefinition	3	AN	(801,802,803,804,805,806,807,810,811,812,813)		See note 28
B.4.k.5.6	drugcumulativedosagenumb	10	N			
B.4.k.5.7	drugcumulativedosageunit	3	N	[001-032]	Mandatory if B.4.k.5.6 is not NULL	See note 28
B.4.k.6	drugdosagetext	100	AN			
B.4.k.7	drugdosageform	100	AN	Lookup on Dosage forms (warning)		See note 12
B.4.k.8	drugadministrationroute	3	N	[001-067] See appendix A5 ICH E2M EWG document[14]		
B.4.k.9	drugparadministration	3	N	[001-067] See appendix A5 ICH E2M EWG document		
B.4.k.10a	reactiongestationperiod	3	N			
B.4.k.10b	reactiongestationperiodunit	3	N	(802,803,804,810)	Mandatory if B.4.k.10a is not NULL	See note 28
B.4.k.11a	drugindicationmeddraversion	8	AN	x.x	Mandatory if B.4.k.11b is not NULL	See note 4
B.4.k.11b	drugindication	250	N	Lookup on MedDRA LLT		See note 4
B.4.k.12a	drugstartdateformat	3	N	(102,610,602)	Mandatory if	See note 1

[14] ICH M2 EWG – Electronic Transmission of Individual Case Safety Report Message Specification (ICH ICSR DTD Version 2.1), Final Version 2.3, Document Revision February 1, 2001. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
					B.4.k.12b not NULL	
B.4.k.12b	drugstartdate	8	N	Date		Should precede B.4.k.14b and conform to B.4.k.12a. See note 15
B.4.k.13.1a	drugstartperiod	5	N			
B.4.k.13.1b	drugstartperiodunit	3	N	[801-807]	Mandatory if B.4.k.13.1a is not NULL	See note 28
B.4.k.13.2a	druglastperiod	5	N			
B.4.k.13.2b	druglastperiodunit	3	N	[801-807]	Mandatory if B.4.k.13.2a is not NULL	See note 28
B.4.k.14a	drugenddateformat	3	N	(102,610,602)	Mandatory if B.4.k.14b not NULL	See note 1
B.4.k.14b	drugenddate	8	N	Date		Should follow B.4.k.12b and conform to B.4.k.14a. See note 15
B.4.k.15a	drugtreatmentduration	5	N			
B.4.k.15b	drugtreatmentdurationunit	3	N	[801-806]	Mandatory if B.4.k.15a is not NULL	See note 28
B.4.k.16	actiondrug	1	N	(1,2,3,4,5,6) 1=Drug withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Unknown 6=Not applicable		
B.4.k.17.1	drugrecurreadministration	1	N	(1,2,3) 1=Yes 2= No 3 = Unknown		
B.4.k.17.2	**drugrecurrence**					**(0...∞)** See note 6
B.4.k.17.2a	drugrecuractionmeddraversion	8	AN	x.x	Mandatory if B.4.k.17.2b is not NULL	See note 4
B.4.k.17.2b	drugrecuraction	250	N	Lookup on MedDRA LLT	Mandatory if the section drugrecurrence is specified	See note 4 and 6
B.4.k.18	**drugreactionrelatedness**					**(0...∞)** **See note 22**
B.4.k.18.1a	drugreactionassesmeddraversion	8	AN	x.x	Mandatory if B.4.k.18.1b is not NULL. Mandatory for any transmission to EVCTM for any medicinal product with B.4.k.1 values = (1) *suspect* or (3) *interacting*	It should be the same as B.2.i.2.a. See note 4 and 23
B.4.k.18.1b	drugreactionasses	250	N	Lookup on MedDRA LLT	Mandatory for any transmission to EVCTM for any	It should be the same as one specified in B.2.i.1.b.

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
					medicinal product with B.4.k.1 values = (1) *suspect* or (3) *interacting*	For transmission to EVCTM, it should be the same as any one of the codes specified in B.2.i.1.b. See note 4 and 23
B.4.k.18.2	drugassessmentsource	60	AN			The accepted value is (1) or (2) or (3) when the value in B.4.k.18.3 is (EVCTM). See note 24
B.4.k.18.3	drugassessmentmethod	35	AN			For transmission to EVCTM, at least one of B.4.k.18.3 values for each event/reaction should be (EVCTM). See note 25
B.4.k.18.4	drugresult	35	AN			For transmission to EVCTM, the accepted value is (1) or (2) when the value in B.4.k.18.3 is (EVCTM). See note 26
B.4.k.19	drugadditional	100	AN			
B.5	**summary**					
B.5.1	narrativeincludeclinical	20000	AN			
B.5.2	reportercomment	500	AN			
B.5.3a	senderdiagnosismeddraversion	8	AN	x.x	Mandatory if B.5.3b is not NULL.	See note 4
B.5.3b	senderdiagnosis	250	N	Lookup on MedDRA LLT		See note 4
B.5.4	sendercomment	2000	AN			

C.2 Rules applicable to EVPM only

The following table (Table 10) presents the list of the business rules applicable to EVPM exclusively, including those presented in Appendix A generating error messages and in Appendix B generating warning messages.

Table 10. List of all business rules applicable to EVPM exclusively

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
A.1.4	Reporttype	1	N	(1,2,3,4) 1=Spontaneous 2=Report from study 3=Other 4=Not available to sender (unknown)	Mandatory	See note 8
A.1.5.2	seriousnessdeath	1	N	(1,2) 1=Yes 2=No	If A.1.5.1 value is (1), at least one of the values should be (1). See note 21	Accepted value is (1) for seriousnessdeath criterion if one of B.2.i.8 value is (5). See note 9
A.2.3.3	Observestudytype	1	N	(2,3) 2=Individual	Mandatory if A.1.4 value is	See note 8

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
				patient use 3=Other studies	(2)	
B.4.k.2.2	activesubstancename	100	AN	Lookup on Substances (warning)	Mandatory for any transmission to EVPM (warning) when the value in B.4.k.1 is (1) or (3)	At least one of B.4.k.2.1-B.4.k.2.2 (error). See note 2

C.3 Rules applicable to EVCTM only

The following table (Table 11) summarises the list of the business rules applicable to EVCTM exclusively, including those presented in Appendix A generating error messages and in Appendix B generating warning messages.

Table 11. List of all business rules applicable to EVCTM exclusively

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
A.1.4	reporttype	1	N	(2) 2=Report from study	Mandatory	See note 8
A.2	**primarysource**				**Mandatory**	**(1...∞)** See note 17
A.2.3.1	studyname	100	AN		Mandatory	See notes 13 and 17
A.2.3.2	sponsorstudynumb	35	AN		Mandatory	See note 17
A.2.3.3	observestudytype	1	N	(1) 1=Clinical trials	Mandatory	See notes 8 and 17
B.4.k.2.2	activesubstancename	100	AN	Lookup on Substances (warning)	Mandatory for any transmission to EVCTM (error) when the value in B.4.k.1 is (1) or (3)	At least one of B.4.k.2.1 and B.4.k.2.2 (error). See note 2
B.4.k.18	**drugreactionrelatedness**					**(1...∞)** **See note 22**
B.4.k.18.1a	drugreactionassesmeddraversion	8	AN	x.x	Mandatory for any transmission to EVCTM for any medicinal product with B.4.k.1 values = (1) *suspect* or (3) *interacting*	It should be the same as B.2.i.2.a. See note 4 and 23
B.4.k.18.1b	drugreactionasses	250	N	Lookup on MedDRA LLT	Mandatory for any transmission to EVCTM for any medicinal product with B.4.k.1 values = (1) *suspect* or (3) *interacting*	It should be the same as one specified in B.2.i.1.b. For transmission to EVCTM, it should be the same as any one of the codes specified in B.2.i.1.b. See note 4 and 23
B.4.k.18.2	drugassessmentsource	60	AN			The accepted value is (1) or (2) or (3) when the value in B.4.k.18.3 is (EVCTM).

DATA ELEMENT	DTD DESCRIPTOR	MAX LENGTH	TYPE	VALUES	MANDATORY	NOTES
						See note 24
B.4.k.18.3	drugassessmentmethod	35	AN			For transmission to EVCTM, at least one of B.4.k.18.3 values for each event/reaction should be (EVCTM). See note 25
B.4.k.18.4	drugresult	35	AN			For transmission to EVCTM, the accepted value is (1) or (2) when the value in B.4.k.18.3 is (EVCTM). See note 26

C.4 Notes:

1. **Date Format Codes**

102 = CCYYMMDD	*(example: 12 JANUARY 1997 14:02:17 --> 19970112)*
203 = CCYYMMDDHHMM	*(example: 12 JANUARY 1997 14:02:17 --> 199701121402)*
204 = CCYYMMDDHHMMSS	*(example: 12 JANUARY 1997 14:02:17 --> 19970112140217)*
610 = CCYYMM	*(example: 12 JANUARY 1997 14:02:17 --> 199701)*
602 = CCYY	*(example: 12 JANUARY 1997 14:02:17 --> 1997)*

2. ***medicinalproduct* and *activesubstancename***

The presence of at least one of the data elements *medicinalproduct* (ICH E2B(R2) B.4.k.2.1) or *activesubstancename* (ICH E2B(R2) B.4.k.2.2) is mandatory. In each drug section at least one of these data elements should be populated, otherwise the validation performed by EV generates an error.

For combination products, the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) needs to be repeated for each active substance as necessary.

Where medicinal products cannot be described on the basis of the active substance(s) or the invented name, e.g. in case only the therapeutic class is reported by the primary source, or in case of other administered therapies that cannot be structured, this information should be reflected in the data element *narrativeincludeclinical* (ICH E2B(R2) B.5.1).

For cases submitted to EVCTM, the population of the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) is mandatory when the value in the data element *drugcharacterisation* (ICH E2B(R2) B.4.k.1) is '1' (suspect) or '3' (interacting). Failure of this validation generates an error.

Warning refers to the following validations:

- The failure of a successful match of data elements *medicinalproduct* (ICH E2B(R2) B.4.k.2.1), *patientdrugname* (ICH E2B(R2) B.1.8.a) and *parentdrugname* (ICH E2B(R2) B.1.10.8.a) with the EVMPD lookup on medicinal products generates a warning;
- The failure of a successful match of data elements *activvesubstancename* (ICH E2B(R2) B.4.k.2.2) with the EVMPD lookup on active substances generates a warning. However, for cases submitted to EVCTM, for which it is not possible to recode against EVMPD active substance names or codes

provided in the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) and characterised as suspect or interacting, line listings of those cases will be sent regularly to sponsors of interventional clinical trials. Action to populate EVMPD with investigational medicinal products information not already included and to resubmit the corrected cases should take place immediately and no later than 15 days following the receipt of the listings;

- For cases submitted to EVPM, the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) should be populated when the value in the data element *drugcharacterisation* (ICH E2B(R2) B.4.k.1) is '1' (suspect) or '3' (interacting). Failure of this validation generates a warning.

3. ***companynum* and *authoritynumb***

There should be only one of these 2 data elements *authoritynumb* (ICH E2B(R2) A.1.10.1) or *companynumb* (ICH E2B(R2) A.1.10.2) provided in each report. The system generates an error if none of these data element or both of them are populated. The value in these data elements should be a concatenation of 'primary source country code-company or regulator name-report number'. Each component should be separated by a hyphen. The value should always start with a 'valid ISO3166 country code-'. Failure of the validation of the first part of the concatenation ('valid ISO3166 country code-') generates an error message. Any information concerning previous transmissions of the same case from other senders should be provided in the section Other case identifiers in previous transmissions (ICH E2B(R2) A.1.11) where applicable.

4. **MedDRA Version**

The supported MedDRA versions are related to the EV environment (EV compliance testing environment or production environment) that is the target of the Safety Message transmission. It also relates to the current MedDRA version officially published by the MedDRA Maintenance Support Service Organisation (MSSO). The EV compliance testing environment supports MedDRA version 4.0 and higher. The EV production environment supports the previous and the current MedDRA version. The validation process of the ICSRs accepts only current LLT numeric codes of the supported MedDRA versions. All stakeholders should follow the recommendations of the MedDRA MSSO regarding the switch to a new MedDRA version. The latest supported MedDRA versions in line with the official semi annual releases are posted on the EudraVigilance website. The use of non-valid numeric MedDRA codes generates an error message in the validation process (except in the data element *testname* (ICH E2B(R2) B.3.1c) where valid MedDRA LLT names are also accepted).

For the ICSRs to be transmitted as part of the retrospective population of EudraVigilance and for the periodic transmission of ICSRs, as outlined in Part III of Volume 9A of The Rules Governing Medicinal Products in the European Union, the fields requiring MedDRA coding will accept LLT numeric codes of MedDRA version 4.0 or higher.

5. ***sendertelextension*, *senderfaxextension*, *receivertelextension*, *receiverfaxextension***

If the length is greater than 5 characters the system generates a warning, otherwise if it is greater than 10 characters the system generates an error.

6. ***drugrecurrence section* and *drugrecuraction***

The section *drugrecurrence* (E2B(R2) B.4.k.17.2) is not mandatory. The data element *drugrecuraction* (E2B(R2) B.4.k.17.2b) becomes mandatory if the section *drugrecurrence* is specified.

7. ***reactionmeddrapt***

The system does not check the MedDRA preferred terms (PTs) reported in the data element *reactionmeddrapt* (ICH E2B(R2) B.2.i.2.b). The EV system does not store this information. The EV

system links the specified LLT to the MedDRA hierarchy, which allows subsequently the appropriate association with the corresponding PT(s).

8. ***reporttype* and *observestudytype***

Any transmissions to EV (EVPM or EVCTM) require the data element *reporttype* (ICH E2B(R2) A.1.4) and the data element *observestudytype* (ICH E2B(R2) A.2.3.3) to be correctly specified, as described in Appendixes A.2 and A.3, in order to obtain a successful outcome of the validation of the ICSRs. Failure of the validation generates an error message.

a) For ICSRs sent to EVPM:

- When the value of the data element *reporttype* (ICH E2B(R2) A.1.4) is '2' (report from study), the data element *observestudytype* (ICH E2B(R2)A.2.3.3) should not be NULL and the accepted values are '2' (individual patient use) or '3' (other studies).
- When the value of the data element *observestudytype* (ICH E2B(R2)A.2.3.3) is '2' (individual patient use) or '3' (other studies), the accepted value for the data element *reporttype* (ICH E2B(R2) A.1.4) is '2' (report from study).
- *Primarysource* (ICH E2B(R2) A.2) iterations are repeatable sections. Therefore, when mandatory, the data element *observestudytype* (ICH E2B(R2) A.2.3.3) needs to be specified in at least one section.

b) For SUSARs sent to EVCTM:

- The accepted value for the data element *reporttype* (ICH E2B(R2) A.1.4) is '2' (report from study). The data element *observestudytype* (ICH E2B(R2)A.2.3.3) should not be NULL and the accepted value is '1' (clinical trial).

When follow-up information impacts on the type of report or the type of study, the report should always be reclassified with the most specific information. For example,

- When an ICSR is initially submitted with the value '1' (spontaneous report) in the data element *reporttype* (ICH E2B(R2) A.1.4), it should be reclassified with the value '2' (report from study) if this information is available in the follow-up report and the data element *observestudytype* (ICH E2B(R2)A.2.3.3) should be populated with the appropriate value.
- When an ICSR is initially submitted to EVPM with the value '2' (individual patient use) or '3' (other studies) in the data element *observestudytype* (ICH E2B(R2)A.2.3.3), it should be reclassified with the value '1' (clinical trial) if this information is available in the follow-up report. The corresponding follow-up ICSR should be submitted to EVCTM. No nullification of the initial report should be done in EVPM.

9. ***seriousnessdeath* and *reactionoutcome***

Any ICSR submitted to EVPM and EVCTM with the seriousness criterion 'results in death' (value '1' in the data element *seriousnessdeath* (ICH E2B(R2) A.1.5.2)) should have at least one reaction with an outcome 'fatal' (value '5' in the data element *reactionoutcome* (ICH E2B(R2) B.2.i.8)).

Failure of this validation will generate an error message.

Any ICSR submitted to EVPM with at least one reaction with the outcome 'fatal' (value '5' in the data element *reactionoutcome* (ICH E2B(R2) B.2.i.8)), should have the seriousness criterion 'results in death' populated with the value '1' (yes) in the data element *seriousnessdeath* (ICH E2B(R2) A.1.5.2). This validation does not apply to EVCTM.

If the death is unrelated to the reported reaction(s), only the section *patientdeath* (ICH E2B(R2) B.1.9) should be completed. The outcome of the reaction(s) reported in the data element *reactionoutcome* (ICH E2B(R2) B.2.i.8) should not be 'fatal' and the seriousness criterion in the data element (ICH E2B(R2) A.1.5.2) should not be flagged as 'results in death'.

10. ***qualification* and *medicallyconfirm***

At least one primary source included in the repeatable section *primarysource* (ICH E2B(R2) A.2) should have information regarding the qualification of the primary source reported in the data elements *qualification* (ICH E2B(R2) A.2.1.4) with one of the following numerical values: '1' (physician), '2' (pharmacist), '3' (other health professional), '4' (lawyer) or '5' (consumer or a non-health professional).

Failure to comply with this validation will generate an error report. This is a temporary measure to be applied for a 12-month period from the date of publication of this guidance, in order to allow stakeholders the possibility to update their system. Following this transitional period any primary source included in the repeatable section *primarysource* (ICH E2B(R2) A.2) should have a qualification reported in the data elements qualification (ICH E2B(R2) A.2.1.4).

The data element *medicallyconfirm* (ICH E2B(R2) A.1.14) should be populated if the **INITIAL** Case Report is reported by a non-health professional. The following recommendations should be followed:

a) First primary source is a non-health professional

- In the INITIAL Case Report, the value in the data element *medicallyconfirm* (ICH E2B(R2) A.1.14) should be '2' (No) and the value reported in the data element qualification (ICH E2B(R2) A.2.1.4) should be '4' (lawyer) or '5' (consumer or a non-health professional).
- In subsequent FOLLOW-UP Case Report(s), the value of the data element *medicallyconfirm* (ICH E2B(R2) A.1.14) should be '1' (yes), only if any additional information has been reported by a health professional suspecting a causal relationship between the drug and the reported reaction. In addition, one of the values reported in the data element *qualification* (ICH E2B(R2) A.2.1.4) of the repeatable Primary Source(s) Information section should be '1' (physician), '2' (pharmacist) or '3' (other health professional).

b) First primary source is a health professional

- In the INITIAL Case Report, the data element *medicallyconfirm* (ICH E2B(R2) A.1.14) should not be populated and the value reported in the data element *qualification* (ICH E2B(R2) A.2.1.4) should be '1' (physician), '2' (pharmacist) or '3' (other health professional).
- In the subsequent FOLLOW-UP Case Report(s), the value of the data element *medicallyconfirm* (ICH E2B(R2) A.1.14) should remain empty.

The Primary Source(s) Information section (ICH E2B(R2) A.2) is repeatable to allow entry of information for several reporters.

Examples

- When a case is initially reported by a consumer and subsequent follow-up information has been reported by a health professional suspecting a causal relationship between the reported medicinal product and the reaction, the Primary Source(s) Information section (ICH E2B(R2) A.2) should be repeated to enter both the consumer information and the health professional information. In this example, the value of the data element *medicallyconfirm* (ICH E2B(R2) A.1.14) should be '1' (yes).
- If a case has been initially reported by a consumer and follow-up information has been reported by a lawyer and no information has been received from a health professional, the Primary Source(s)

Information section (ICH E2B(R2) A.2) should be repeated to enter both non-health professional information and the value of the data element *medicallyconfirm* (ICH E2B(R2) A.1.14) should be '2' (no).

- When a consumer submits medical documentation that supports the occurrence of the adverse reaction and which indicates that a health professional suspects a causal relationship between the reported medicinal product and the reaction, this should be considered as a medically confirmed report. In this context the Primary Source(s) Information section (ICH E2B(R2) A.2) should be repeated to enter both the consumer information and the health professional information and the value of the data element *medicallyconfirm* (ICH E2B(R2) A.1.14) should be '1' (yes).
- When a case is initially reported by a health professional and additional information is then received from a consumer, the Primary Source(s) Information section (ICH E2B(R2) A.2) should be repeated to enter both the health professional information and the consumer information and the data element *medicallyconfirm* (ICH E2B(R2) A.1.14) should remain empty.
- When a case is initially reported by a consumer and subsequent follow-up information has been reported by a health professional denying a causal relationship between the drug and the reported reaction, the Primary Source(s) Information section (ICH E2B(R2) A.2) should be repeated to enter both the consumer information and the health professional information. In this example, the value of the data element *medicallyconfirm* (ICH E2B(R2) A.1.14) should be '2' (no).

11. **patient/parent's age, height or weight**

If the patient/parent's age, height or weight value is above the allowed upper limit, the relevant ICH E2B(R2) data element should remain empty and the information should be reported in the data element *narrativeincludeclinical* (ICH E2B(R2) B.5.1). Reported values above the upper limits generate an error message.

12. ***drugdosageform***

If data element drugdosageform (ICH E2B(R2) B.4.k.7) is not null, the failure of a successful match with the latest version of the European Pharmacopoeia Dosage Forms list generates a warning.

See http://eudravigilance.emea.europa.eu/human/PharmaceuticalDoseFormsUpdate.asp (or http://eudravigilance.ema.europa.eu/human/PharmaceuticalDoseFormsUpdate.asp) for the version currently implemented in EudraVigilance. If the drug dosage form is not available in the latest version of the European Pharmacopoeia Dosage Forms list or is under proposal, the information should only be entered in the data element *narrativeincludeclinical* (ICH E2B(R2) B.5.1).

13. ***studyname***

For any transmission to EVCTM, the data element *studyname* (ICH E2B(R2) A.2.3.1) should contain the following concatenations:

a) For SUSARs originating within the EEA:

- 'Valid EudraCT Number#Study abbreviated name' when the values in the data elements *primarysourcecountry* (ICH E2B(R2) A.1.1) and *occurcountry* (ICH E2B(R2) A.1.2) are EEA countries. Failure to enter a EudraCT Number validated against the EudraCT database will generate an error message.

b) For SUSARs originating outside the EEA:

- 'Valid EudraCT Number#Study abbreviated name' (if the clinical trial is authorised in the EEA or is contained in an agreed Paediatric Investigation Plan) or

- `#Study abbreviated name' (if the clinical trial is conducted exclusively outside the EEA or is not contained in an agreed Paediatric Investigation Plan),

  when the values in the data elements *primarysourcecountry* (ICH E2B(R2) A.1.1) and *occurcountry* (ICH E2B(R2) A.1.2) are non-EEA countries.

A valid EudraCT Number should match with an authorised number in the EudraCT database and should have the format YYYY-NNNNNN-CC, where

- YYYY is the year in which the number has been issued,
- NNNNNN is a six digit sequential number,
- CC is a check digit.

The following generic EudraCT Number is provided for all interventional clinical trials including a centre in a Member State and started before 01 May 2004 (or before the clinical trial Directive 2001/20/EC has been implemented in a Member State): **EVCT-000000-16**. It should be used in the data element *studyname* (ICH E2B(R2) A.2.3.1 for these interventional clinical trials only. It should be followed by the `#' symbol and the study abbreviated name.

ICSRs originating from interventional clinical trials, which need to be reported by MAHs to EVCTM in accordance with the requirements described in Volume 9A of the Rules Governing Medicinal Products in the European Union, should include the following generic EudraCT number **EVCT-999999-25**, followed by the `#' symbol and the study abbreviated name. This is to be able to exclude these ICSRs from the 7 days expedited reporting compliance monitoring. It should be used in the data element *studyname* (ICH E2B(R2) A.2.3.1 for cases which occurred outside the EEA in interventional clinical trials for which the sponsor has **NO** reporting obligation of these cases in the EEA under the Directive 2001/20/EC.

When the sponsor does have clinical trials ongoing in the EEA with the same IMP, the reports of SUSARs from third country trials not authorised in the EEA should be submitted to EVCTM in accordance with the Directive 2001/20/EC. The 7 days reporting requirements for fatal and life threatening SUSARs apply. The recommendations detailed in point b) above should be followed.

It is important to maintain the structure of the concatenation with the `#' symbol (`YYYY-NNNNNN-CC#Study abbreviated name' or `#Study abbreviated name') in the data element *studyname* (ICH E2B(R2) A.2.3.1) to obtain a successful outcome of the validation of this data element. Failure of the validation on the first part of the reported data (`YYYY-NNNNNN-CC#' or `#') will generate an error message. Any local clinical trial numbers (used to identify clinical trials at national levels) should be entered in the data elements *sendercomment* (ICH E2B(R2) B.5.4).

The data element *studyname* (ICH E2B(R2) A.2.3.1) is limited to 100 characters. If necessary the study name should be abbreviated in the concatenation. The entire study name can be included in the data element *narrativeincludeclinical* (ICH E2B(R2) B.5.1).

14. **Lookups on test name**

The ICSRs including tests should report in the data element *testname* (ICH E2B(R2) B.3.1c) a valid MedDRA LLT name or code. The failure of a successful match with the MedDRA lookup generates an error. If necessary, test names and results can be provided in free text in the data element *resultstestsprocedures* (ICH E2B(R2) B.3.2).

15. **Dates**

- Dates should be valid. They should conform to the corresponding date format (See note 1) and no date/time value should exceed the current UK GMT time plus 12 hours. Failure of the validation of the date format generates an error.

- All dates~~, except the values in the data elements *messagedate* (ICH M2 M.1.7b) and *transmissiondate* (ICH E2B(R2) A.1.3b),~~ should be inferior or equal to the ~~value in the data element *receiptdate* (ICH E2B(R2) A.1.7b)~~ EudraVigilance Gateway date. Failure of this validation generates an error.
- Each start date entered in the data elements *patientmedicalstartdate* (ICH E2B(R2) B.1.7.1c), *patientdrugstartdate* (ICH E2B(R2) B.1.8c), *parentmedicalstartdate* (ICH E2B(R2) B.1.10.7.1c), *parentdrugstartdate* (ICH E2B(R2) B.1.10.8c), *reactionstartdate* (ICH E2B(R2) B.2.i.4b) and *drugstartdate* (ICH E2B(R2) B.1.8c) should be inferior or equal to the specified end date. Failure of this validation generates an error.
- Each end date entered in the data elements *patientmedicalenddate* (ICH E2B(R2) B.1.7.1f), *patientdrugenddate* (ICH E2B(R2) B.1.8e), *parentmedicalenddate* (ICH E2B(R2) B.1.10.7.1f), *parentdrugenddate* (ICH E2B(R2) B.1.10.8e), *reactionenddate* (ICH E2B(R2) B.2.i.5b), *drugenddate* (ICH E2B(R2) B.4.k.14b) should be superior or equal to the specified start date. Failure of this validation generates an error.

16. ***primarysourcecountry* and *occurcountry***

The primary source country reported in the data element (ICH E2B(R2) A.1.1) is the country of the main primary source who reports the fact. It should correspond to one of the primary source countries reported in the data element *reportercountry* (ICH E2B(R2) A.2.1.3). All the *primarysource* (ICH E2B(R2) A.2) iterations are repeatable to allow entry of information for several reporters. For cases described in the world-wide literature, the country of the first author of the literature article should be used as the primary source country. In case the country of occurrence is different from the primary source country, this should be entered in the data element *occurcountry* (ICH E2B(R2) A.1.2).

17. **EVCT-ICSR**

Primarysource (ICH E2B(R2) A.2) iterations are repeatable sections. Therefore the data elements *studyname* (ICH E2B(R2) A.2.3.1), *sponsorstudynumb* (ICH E2B(R2) A.2.3.2) and *observestudytype* (ICH E2B(R2) A.2.3.3) need to be specified in at least one section for each EVCT-ICSR.

The EVCT-ICSR will only be accepted by EVCTM if these data elements are reported in at least one primary source section. If provided in more than one primary source section, the information in these data elements should be the same between each primary source section. Failure to this validation will generate an error report.

18. ***messagereceiveridentifier***

When submitting a Safety Message to EV, the value accepted in the data element *messagereceiveridentifier* (ICH M2 M.1.5) is one of the following, depending to which module the message is addressed:

- 'EVTEST' (Test environment – EVPM)
- 'EVHUMAN' (Production environment – EVPM)
- 'EVCTMTEST' (Test environment – EVCTM)
- 'EVCTMPROD' (Production environment – EVCTM).

19. ***messagetype***

When submitting a Safety Message to EV, the value accepted in the data element *messagetype* (ICH M2 M.1.1) is one of the following:

- 'ichicsr' for expedited ICSRs submitted to EVPM or EVCTM;

- 'backlog' for retrospective ICSRs submitted to EVPM. This allows the exclusion of these reports from expedited reporting compliance checks. Separate business rules apply for the retrospective population of EVPM. They are described in Part III of Volume 9A of the Rules Governing Medicinal Products in the European Union;
- 'backlogct' for retrospective ICSRs submitted to EVCTM. This allows the exclusion of these reports from expedited reporting compliance checks;
- 'psur' for the periodic transmission of ICSRs not transmitted on an expedited basis in electronic format to EVPM;
- 'ctasr' for the periodic transmission of ICSRs not transmitted on an expedited basis in electronic format to EVCTM.

The value in the data element *messagetype* (ICH M2 M.1.1) is case-sensitive and should be reported in lower case.

20. ***casenullification***

No follow-up report can be submitted for cases which have been previously nullified. When an ICSR contains the value '1' (yes) in the data element *casenullification* (ICH E2B(R2) A.1.13), an error message will be generated for any additional follow-up report submitted for this case. A new case with a different 'Worldwide unique case identification number' (data element *authoritynumb* (ICH E2B(R2) A.1.10.1) or *companynumb* (ICH E2B(R2) A.1.10.2)) should be created and submitted if necessary.

21. ***Serious*** **and** ***seriousness***

The population of the data elements *serious* (ICH E2B(R2) A.1.5.1) is mandatory.

~~The population of the data elements *seriousness* (ICH E2B(R2) A.1.5.2) is mandatory when the value in the data element *serious* (ICH E2B(R2) A.1.5.1) is '1' (yes).~~

At least one of the data elements *seriousness* (ICH E2B(R2) A.1.5.2) should be populated with the value '1' (yes) when the data elements *serious* (ICH E2B(R2) A.1.5.1) is populated with the value '1' (yes). The remaining fields of the data elements *seriousness* (ICH E2B(R2) A.1.5.2) can have the values '1' (yes), '2' (no) or be left empty.

If one of the data elements *seriousness* (ICH E2B(R2) A.1.5.2) contains the value '1' (yes), the data element *serious* (ICH E2B(R2) A.1.5.1) should be populated with the value '1' (yes).

Failure to these validations will generate an error message.

22. ***Section drugreactionrelatedness*** **(ICH E2B (R2) B.4.k.18)**

This section provides the means to transmit the degree of suspected relatedness of each reported medicinal product to each reported event/reaction.

The repeatable subsections should be used to submit the assessment of the causality of each reported medicinal product classified as suspect or interacting for each reported event/reaction.

The repeatable subsections allow for the assessment to be provided for different sources of information. They also give the option to apply other methods of causality assessment in addition to the mandatory binary decision method described in Note 25.

23. **Data element *drugreactionasses* (ICH E2B (R2) B.4.k.18.1)**

Each individual event/reaction reported in the ICSR should have a causality assessment assigned for each reported medicinal product classified as suspect or interacting. This section should contain all the same MedDRA LLT code(s) as the one(s) reported in the data element *reactionmeddrallt* (ICH E2B(R2)

B.2.i.1.b). The reported MedDRA version should be identical as the one detailed in the data element *reactionmeddraversionllt* (ICH E2B(R2) B.2.i.2.a).

24. **Data element *drugassessmentsource* (ICH E2B (R2) B.4.k.18.2)**

This data element allows to the identification of the source of assessment (Investigator, Sponsor, NCA) of the causality provided for each event/reaction reported in ICSRs.

A controlled vocabulary has been introduced in order to avoid error reporting. Only numerical values, as presented in Table 12, are accepted in the data element *drugassessmentsource* (ICH E2B (R2) B.4.k.18.2) when the value in the data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) is 'EVCTM'.

Table 12. Accepted values in the data element *drugassessmentsource* (ICH E2B (R2) B.4.k.18.2) when the value in the data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) is 'EVCTM'

SOURCE OF ASSESSMENT (ICH E2B (R2) B.4.k.18.2)	VALUE
Investigator	1
Sponsor	2
NCA	3

25. **Data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3)**

Numerous methods of causality assessment of adverse drug reactions have been published in the literature and are currently used worldwide[15]. Based on this principle, ICH E2B(R2) allows the possibility to provide several results of causality assessment by using one or more methods of assessment.

At least one method of assessment corresponding to the binary decision method detailed in the CIOMS Working Group VI report[16] should be provided for each reported adverse event/reaction. The binary decision method ('Reasonable possibility' or 'No reasonable possibility'), should be used to report the causal association between each reported medicinal product classified as suspect or interacting and each reported event/reaction. This method of assessment should be characterised with the value 'EVCTM' in the data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3). The use of other methods of causality assessment is optional. Table 14 provides examples on how to populate this data element.

26. **Data element *drugresult* (ICH E2B (R2) B.4.k.18.4)**

This data element is used to submit the result of the causality assessment of each medicinal product classified as suspect or interacting for each event/reaction reported in the ICSR.

A controlled vocabulary has been introduced in order to avoid error reporting when providing a causality assessment result in accordance with the binary decision method described in Note 25. Only numerical values, as presented in Table 13, are accepted in the data element *drugresult* (ICH E2B (R2) B.4.k.18.4) when the value in the data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) is 'EVCTM'.

[15] Methods of causality assessment of adverse drug reaction. A systematic review; Agbabiak T.B., Savovic J., Ernst E. Drug Safety 2008: 31(1): 21-37.
[16] Management of Safety Information from Clinical Trials CIOMS Working Group VI (CIOMS, Geneva 2005).

When using other methods of causality assessment, the sponsor should decide which categories of causality assessment result correspond to 'Reasonable possibility' and which ones refer to 'No reasonable possibility'.

Table 13. Accepted values in the data element *drugresult* (ICH E2B (R2) B.4.k.18.4) when the value in the data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) is 'EVCTM'

RESULT OF ASSESSMENT (ICH E2B (R2) B.4.k.18.4)	VALUE
Reasonable possibility	1
No reasonable possibility	2

Each MedDRA LLT code reported in the data element *reactionmeddrallt* (ICH E2B(R2) B.2.i.1.b) should have an assessment provided by the Investigator AND/OR by the Sponsor for each reported medicinal product classified as suspect or interacting. Failure to comply with this requirement generates an error report.

Any initial ICSR should contain at least one reaction with a causality assessment 'Reasonable possibility' (based on the binary decision method detailed in the CIOMS Working Group VI report) to at least one of the reported medicinal products classified as suspect or interacting. If this information is not available, the ICSR submitted to EVCTM is classified as an error report and requires correction and resubmission if applicable. This rule is not applied to follow-up ICSRs submitted to EVCTM in order to allow to sponsors the possibility to downgrade the causality of an initial ICSR.

Examples on how to provide information on causality assessment are provided in Table 14.

When the sponsor is sending the report at an early stage and does not have sufficient information to assign causalities between the reported medicinal products classified as suspect or interacting and the reported adverse events/reactions, a 'Reasonable possibility' of causal association should be considered until further information is available to confirm or downgrade the initially reported causality.

Table 14. Examples of reporting of causality assessment of 2 medicinal products (Medicinal Product A and Medicinal Product B) considered suspect or interacting for 3 events (Event 1, Event 2 and Event 3)

REACTION ASSESSED (ICH E2B (R2) B.4.k.18.1b)	SOURCE OF ASSESSMENT (ICH E2B (R2) B.4.k.18.2) a	METHOD OF ASSESSMENT (ICH E2B (R2) B.4.k.18.3) b	RESULT OF ASSESSMENT (ICH E2B (R2) B.4.k.18.4) c	INFORMATION TO BE REPORTED TO EVCTM b
k(1) = Medicinal Product A (considered suspect or interacting) [d]				
Event 1 LLT MedDRA code	Investigator	Expert judgment	Definite	Optional
Event 1 LLT MedDRA code	Sponsor	Algorithm	Probable	Optional
Event 1 LLT MedDRA code	**2**	**EVCTM**	**1**	**Mandatory**
Event 2 LLT MedDRA code	Investigator	Expert judgment	Doubtful	Optional
Event 2 LLT MedDRA code	Sponsor	Algorithm	Possible	Optional

REACTION ASSESSED (ICH E2B (R2) B.4.k.18.1b)	SOURCE OF ASSESSMENT (ICH E2B (R2) B.4.k.18.2) a	METHOD OF ASSESSMENT (ICH E2B (R2) B.4.k.18.3) b	RESULT OF ASSESSMENT (ICH E2B (R2) B.4.k.18.4) c	INFORMATION TO BE REPORTED TO EVCTM b
Event 2 LLT MedDRA code	**2**	**EVCTM**	**1**	**Mandatory**
Event 3 LLT MedDRA code	Investigator	Expert judgment	Unrelated	Optional
Event 3 LLT MedDRA code	Sponsor	Algorithm	Excluded	Optional
Event 3 LLT MedDRA code	**2**	**EVCTM**	**2**	**Mandatory**
k(2) = Medicinal Product B (considered suspect or interacting) [d]				
Event 1 LLT MedDRA code	Sponsor	Algorithm	No reasonable possibility	Optional
Event 1 LLT MedDRA code	**2**	**EVCTM**	**2**	**Mandatory**
Event 2 LLT MedDRA code	Investigator	Expert judgment	Unrelated	Optional
Event 2 LLT MedDRA code	NCA	Algorithm	Possible	Optional
Event 2 LLT MedDRA code	Sponsor	Algorithm	Reasonable possibility	Optional
Event 2 LLT MedDRA code	**2**	**EVCTM**	**1**	**Mandatory**
Event 3 LLT MedDRA code	Investigator	Expert judgment	Definite	Optional
Event 3 LLT MedDRA code	**1**	**EVCTM**	**1**	**Mandatory**

[a] Each reported adverse event/reaction should have at least one causality assessment provided by the Investigator AND/OR by the Sponsor for each reported medicinal product classified as suspect or interacting. The accepted value in the Data element *drugassessmentsource* (ICH E2B (R2) B.4.k.18.2) is '1', '2' or '3' when the value in the Data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) is 'EVCTM'.

[b] At least one method of assessment corresponding to the binary decision method described in Note 25 should be provided for each reported adverse event/reaction. This method should be reported in the data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) with the value 'EVCTM'. Provision in free text of other methods of causality assessment is optional.

[c] The accepted value in the Data element *drugresult* (ICH E2B (R2) B.4.k.18.4) is '1' or '2' when the value in the Data element *drugassessmentmethod* (ICH E2B (R2) B.4.k.18.3) is 'EVCTM'. Provision in free text of results of assessment based on other methods of causality is optional.

[d] The order of the rows is not important since each one represents a complete set of information, however all assessments for the Medicinal Product A (k=1) classified as suspect or interacting

should appear before the assessments for the Medicinal Product B (k=2) classified as suspect or interacting.

27. **Data element *reporterstate* (ICH E2B (R2) A.2.1.2e) and *reporterpostcode* (ICH E2B (R2) A.2.1.2f)**

For cases originating in SPAIN, at least one of the data elements *reporterstate* (ICH E2B (R2) A.2.1.2e) or *reporterpostcode* (ICH E2B (R2) A.2.1.2f) should be populated in accordance with the requirements presented in Appendix H.

28. **Numeric codes for units and intervals**

CODES	UNITS & INTERVALS LIST	CODES	UNITS & INTERVALS LIST
001	kg kilogram(s)	023	Mmol millimole(s)
002	G gram(s)	024	µmol micromole(s)
003	Mg milligram(s)	025	Iu international unit(s)
004	µg microgram(s)	026	Kiu iu(1000s)
005	ng nanogram(s)	027	Miu iu(1,000,000s)
006	pg picogram(s)	028	iu/kg iu/kilogram
007	mg/kg milligram(s)/kilogram	029	Meq milliequivalent(s)
008	µg/kg microgram(s)/kilogram	030	% percent
009	mg/m2 milligram(s)/sq. meter	031	Gtt drop(s)
010	µg/ m2 microgram(s)/ sq. meter	032	Kbq kilobecquerel(s)
011	l litre(s)	800	Decade(s)
012	ml millilitre(s)	801	Year(s)
013	µl microlitre(s)	802	Month(s)
014	Bq becquerel(s)	803	Week(s)
015	GBq gigabecquerel(s)	804	Day(s)
016	MBq megabecquerel(s)	805	Hour(s)
017	Kbq kilobecquerel(s)	806	Minute(s)
018	Ci curie(s)	807	Second(s)
019	MCi millicurie(s)	810	Trimester(s)
020	µCi microcurie(s)	811	Cyclical
021	NCi nanocurie(s)	812	As Necessary
022	Mol mole(s)	813	Total

Appendix D: Medicinal Products and Active Substances Validation

D.1 Validation of Medicinal Products and Active Substances (Automatic Recoding)

Medicinal products and active substances reported in ICSRs are mapped and coded against the EudraVigilance Medicinal Product Dictionary (EVMPD). In this context EVMPD, referred to as 'Reference Source', provides support for data analysis and signal detection in the EudraVigilance Data Warehouse and Analysis System (EVDAS).

The validation of medicinal products and active substances as reported in ICSRs takes place based on the following steps:

1. **Gateway Validation:**

Before any ICSR is loaded in the EudraVigilance database (EVPM or EVCTM), the system checks that it has been received from an authorised sender i.e. an organisation registered with EudraVigilance (Gateway validation).

2. **DTD Validation:**

The content of each field in the ICSRs is further validated to ensure that it contains the correct type of data according to the ICH E2B(R2) guidance and that the data is entered in the correct format (DTD validation).

3. **Business Rules Validation:**

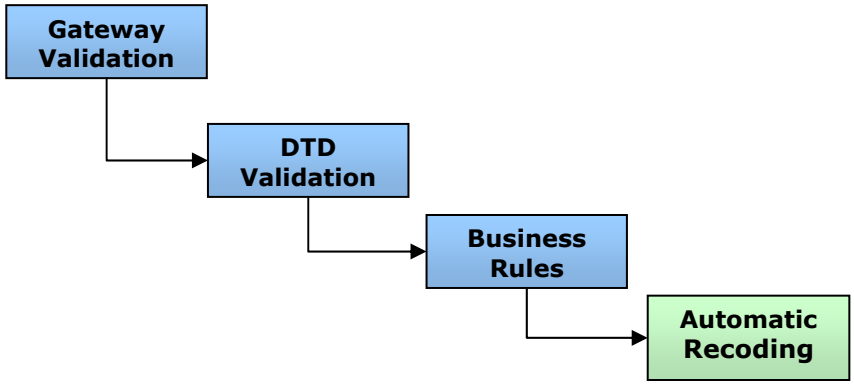
As a next step, several cross checks are performed based on the business rules described in this document (Appendixes A to C).

4. **Automatic Recoding:**

As part of the final step of the validation processes, the medicinal product(s) and active substance(s) reported in the ICSRs are validated against EVMPD to make sure that the information is coded correctly and can be used for data analysis and signal detection in EVDAS. This final step is referred to as Automatic Recoding. If the Automatic Recoding fails the sender is informed by receiving a "Warning" in the acknowledgement message. The ICSR is nevertheless loaded in EV and flagged as 'Not Fully Recoded'.

The ICSRs validation steps performed by the EudraVigilance system are presented in Figure 7.

Figure 7. ICSRs validation steps in EudraVigilance



The ICH E2B(R2) data elements where the Automatic Recoding is performed are listed in Table 15.

Table 15. ICH E2B(R2) data elements with Automatic Recoding

DTD DESCRIPTOR	ICH E2B(R2) DATA ELEMENT	AUTOMATIC RECODING REFERENCE SOURCE
patientdrugname	B.1.8a	EVMPD
parentdrugname	B.1.10.8a	EVMPD
medicinalproduct	B.4.k.2.1	EVMPD
activesubstancename	B.4.k.2.2	EVMPD

The Automatic Recoding is the process of associating unique EVMPD Codes to the medicinal products and active substances reported in ICSRs.

All medicinal products and active substances should be reported the same way as they have been entered in EVMPD in order to be automatically recoded (See D.6-Validation of Medicinal Products Reported in ICSRs and D.7-Validation of Active Substances Reported in ICSRs).

D.2 EVMPD Background and Definitions

The EVMPD version 1.0 was developed by EMA in collaboration with its stakeholders and has been deployed in production in December 2001. In May 2004, EVMPD was extended (EVMPD version 2.0) to include the requirements for the collection, reporting, coding and evaluation of Investigational Medicinal Products (IMPs) as defined in Directive 2001/20/EC and in Volume 10 of The Rules Governing Medicinal Products in the European Union.

The objective of EVMPD is to assist the safety monitoring activities in the EEA by coding medicinal products and active substances in ICSRs, which are reported to EVCTM or to EVPM.

In order to be able to identify each individual medicinal product or active substance in the ICSRs reported to EV, MAHs, Applicants and Sponsors of interventional clinical trials are requested to enter in EVMPD information on the medicinal products for which they hold a marketing authorisation in the EEA / have submitted an application for a marketing authorisation in the EEA, or for which an interventional clinical trial has been authorised in the EEA. The requirements as regards the unique identification of active substances and medicinal products are detailed in Part III of Volume 9A of The Rules Governing Medicinal Products in the European Union and in the detailed Guidance ENTR/CT 4[17].

The EVMPD supports the collection, reporting, coding and evaluation of medicinal product data in a standardised and structured way. In this context the following definitions apply:

1. **Medicinal Product (MP)**

Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances, which may be used in or administered to human beings either with the view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to make a medical diagnosis (Directive 2001/83/EC as amended).

[17] Detailed Guidance on the European Database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module), Revision 1, April 2004 (ENTR/CT 4).

2. **Pharmaceutical Product**

A medicinal product may consist of one or several pharmaceutical products, which are characterised through one or more active substances, the strength of the substances, the pharmaceutical form and one or more routes of administration.

3. **Authorised Medicinal Product (AMP)**

A medicinal product authorised by a Regulatory Authority either within the EEA or outside the EEA.

4. **Investigational Medicinal Product (IMP)**

A pharmaceutical form of an active substance or placebo being tested or used as a reference in an interventional clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form (Directive 2001/20/EC).

5. **Development Medicinal Product (DMP)**

A medicinal product, under investigation in an interventional clinical trial, which does not have a marketing authorisation within the EEA and to which special confidentiality arrangements may need to be applied.

6. **Approved Substance**

Any substance as defined in Directive 2001/83/EC as amended, which is an ingredient of a medicinal product for which a marketing authorisation was granted within or outside the EEA.

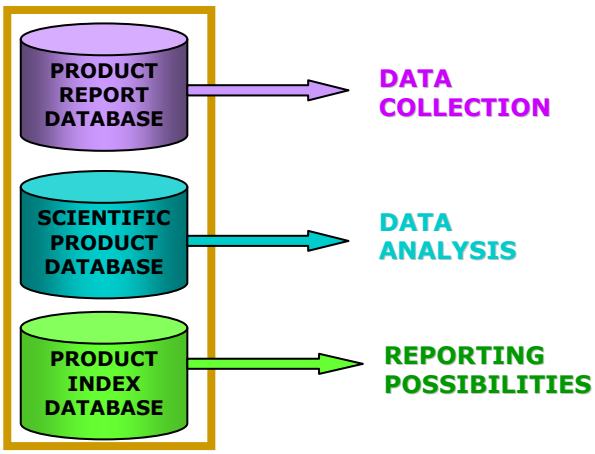
7. **Development Substance**

Any substance under investigation in an interventional clinical trial and which is not contained in any Authorised Medicinal Product (AMP).

D.3 EVMPD Structure

The EVMPD consists of three different databases designed to support the collection, standardisation, coding and scientific evaluation of medicinal products authorised in the EEA and of development medicinal products subject to investigation in interventional clinical trials. The three different databases are presented in Figure 8.

Figure 8. EudraVigilance Medicinal Product Dictionary



1. The **Product Report Database** is designed to support data collection and contains key information related to authorised and development medicinal products, whereby the information is provided by MAHs and Sponsors of interventional clinical trials. The Product Report Database generates the Scientific Product Database and the Product Index Database. Both support the validation and analysis of medicinal products and active substances reported in ICSRs.
2. The **Scientific Product Database** provides a hierarchy for the classification of all medicinal products (either with development or authorised status) registered in EVMPD on the basis of the active substance(s), the strength of the active substance(s) and the pharmaceutical form. The Scientific Product Database allows grouping of medicinal products on the basis of their composition, independent of administrative information such as the invented name and a specific MAH or Sponsor of an interventional clinical trial.

   The hierarchy consists of the following levels:

   - **Abstract Composition**: Each Abstract Composition in the Scientific Product Database represents a group of medicinal products with the same active substance(s);
   - **Abstract Strength**: Each Abstract Strength in the Scientific Product Database represents a group of medicinal products with the same active substance(s) and the same strength of the active substance(s);
   - **Abstract Formulation**: Each Abstract Formulation in the Scientific Product Database represents a group of medicinal products with the same active substance(s) and the same pharmaceutical form;
   - **Abstract Pharmaceutical Product**: Each Abstract Pharmaceutical Product in the Scientific Product Database represents a group of medicinal products with the same active substance(s), the same strength of the active substance(s) and the same pharmaceutical form.
3. The **Product Index Database** serves as a reference ('reporting possibilities') that can be used to report medicinal products and active substances in ICSRs. The Product Index Database contains several 'reporting possibilities' for each medicinal product and for each active substance entered in EVMPD. Each 'reporting possibility' represents a consistent and standardised way to refer to a medicinal product or to an active substance taking into account the possible vagueness of medicinal product information reported by a primary source/reporter in an ICSR. The Product Index Database is generated using the information collected in the Product Report Database (for both authorised and development medicinal products) and the information generated in the Scientific Product Database.

D.4 Product Index Database and 'Reporting Possibilities' for Medicinal Products

D.4.1 Authorised Medicinal Products

For Authorised Medicinal Products the 'reporting possibilities' are created by 'splitting' the medicinal product's Full Presentation Name in defined elements and combining the elements based on a defined algorithm (see Example for Authorised Medicinal Products).

Those defined elements created from the Full Presentation Name are:

- Product Short Name
- Product Generic Name (if applicable)

- Product Strength Name (if applicable)
- Product Form Name (if applicable)
- Product Company Name (if applicable)

The Product Index Database maintains the different 'reporting possibilities' including the Full Presentation Name.

In addition the Product Index Database contains the Abstract Composition(s), Abstract Strength(s), Abstract Formulation(s) and Abstract Pharmaceutical Product(s) generated in the Scientific Product Database from authorised medicinal product. Since approved active substances are sometime reported in the data element *medicinalproduc'* (ICH E2B(R2) B.4.k.2.1), the Product Index Database also contains the Substances Names of the approved substances entered in EVMPD (See D.5.1-Approved Substances).

Example for Authorised Medicinal Product

The following example illustrates how the 'reporting possibilities' are generated in the Product Index Database when an authorised medicinal product is entered in EVMPD.

An authorised medicinal product with the Full Presentation Name 'XYZ Tablets 500 mg', containing acetylsalicylic acid as active substance is entered in the Product Report Database. The Full Presentation Name is 'split' by the owner in the relevant defined elements when entering the information in EVMPD:

- Product Full Presentation Name: XYZ Tablets 500 mg
- Product Short Name (*): XYZ
- Product Generic Name (*): (not applicable)
- Product Company Name (*): (not applicable)
- Product Strength Name (*): 500 mg
- Product Form Name (*) : Tablets

(*) as part of the 'Full Presentation Name'

The Scientific Product Database and the Product Index Database entries are based on the active substance(s), the strength(s) of the active substance(s) and the pharmaceutical form of the authorised medicinal product as detailed in the Summary of Product Characteristic (SmPC).

Based on the SmPC of the medicinal product XYZ Tablets 500 mg, the Scientific Product Database therefore contains the following entries:

- Abstract composition: Acetylsalicylic Acid
- Abstract strength: Acetylsalicylic Acid 500 mg
- Abstract formulation: Acetylsalicylic Acid Tablet
- Abstract pharmaceutical product: Acetylsalicylic Acid Tablets 500 mg

The Product Index Database entries for the product 'XYZ Tablets 500mg' are generated from the Product Report Database and the Scientific Product Database as follows (Each entry is associated to a unique Product Indext Code):

- XYZ (Product Short Name)

- XYZ 500 mg (Product Short Name + Product Strength Name)
- XYZ Tablets (Product Short Name + Product Form Name)
- XYZ 500 mg Tablets (Product Short Name + Product Strength Name + Product Form Name; included only if different from the Product Full Presentation Name)
- XYZ Tablets 500 mg (Product Full Presentation Name)
- Acetylsalicylic Acid (Abstract composition)
- Acetylsalicylic Acid 500 mg (Abstract strength)
- Acetylsalicylic Acid Tablets (Abstract formulation)
- Acetylsalicylic Acid Tablets 500mg (Abstract pharmaceutical product)

The Product Index entries represent the different 'reporting possibilities' in ICSRs submitted to EV for which the Automatic Recoding will be successful.

D.4.2 Development Medicinal Products

For Development Medicinal Products the 'reporting possibilities' are created based on the following elements:

- Product Code (if applicable)
- Product Name (if applicable)
- Product Other Name (if applicable)

These elements appear individually in the Product Index Database. In addition the Abstract Composition(s), Abstract Strength(s), Abstract Formulation(s) and Abstract Pharmaceutical Product(s) generated in the Scientific Product Database from development medicinal products are added to the Product Index Database. Since development substances are sometime reported in the data element 'medicinalproduct' (ICH E2B(R2) B.4.k.2.1), the Product Index Database also contains the Current Names/Codes of development substances entered in EVMPD (See D.5.2-Development Substances).

Example for Development Medicinal Product

The following example illustrates how the 'reporting possibilities' are generated in the Product Index Database when a development medicinal product is entered in EVMPD.

A development medicinal product 'CTX5132/25 Capsules' is entered in the Product Report Database. The development medicinal product reference is 'split' by the owner in the relevant defined elements when entering the information in EVMPD:

- Product Code (*): CTX5132/25
- Product Name(*): (not available)
- Product Other Name(*): (not available)

(*) as part of the investigational medicinal product description in the clinical trial application

The Scientific Product Database and the Product Index Database entries are based on the development substance(s), the strength(s) of the development substance(s) and the pharmaceutical form of the development medicinal product (reference is the clinical trial application). In accordance with the

clinical trial application, the development medicinal product contains the development substance CTX5132 in the form of capsules with the strength of 25 mg.

The Scientific Product Database therefore contains the following entries:

- Abstract composition: CTX5132
- Abstract strength: CTX5132 25 mg
- Abstract formulation: CTX5132 capsule
- Abstract pharmaceutical product: CTX5132 25 mg capsule

The Product Index Database entries for 'CTX5132/25' are generated from the Product Report Database and the Scientific Product Database as follows:

- CTX5132/25 (Product Code)
- CTX5132 (Abstract composition)
- CTX5132 25 mg (Abstract strength)
- CTX5132 capsule (Abstract formulation)
- CTX5132 25 mg capsule (Abstract pharmaceutical product)

These 'reporting possibilities' are confidential, which means that they are only available for reporting by the sponsor organisation of the interventional clinical trial, who entered the development medicinal product in EVMPD.

D.5 Product Index Database and 'reporting possibilities' for active substances

D.5.1 Approved Substances

For Approved Substances the 'reporting possibilities' are generated from the Product Report Database based on the following elements:

- Substance Name
- Substance Translation(s) (of the Substance Name)
- Substance Alias(es) (of the Substance Name), also referred to as "Synonym(s)"
- Alias(es) Translation(s) (of the Substance Name)

See example in Table 16

Table 16. Example of generation of reporting possibilities for approved substances

ELEMENTS	REPORTING POSSIBILITIES
Substance EV Code	SUB09611MIG
Substance Name	Paracetamol [*Reference Source: INN*]
Substance Translations	
Translation	Paracetamolum [*Latin*]
Translation	Paracétamol [*French*]

ELEMENTS	REPORTING POSSIBILITIES
Translation	Paracetamol [*Spanish*]
Translation	Paracetamol [*Portuguese*]
Translation	Paracetamolo [*Italian*]
Substance Aliases	
Alias	Acetaminophen [*Reference Source:Martindale*]
Alias Translation	Acetaminofene [*Italian*]

D.5.2 Development Substances

For Development Substances the 'reporting possibilities' are generated from the Product Report Database based on the following elements:

- Current Name or Code
- Previous Name(s) or Code(s)

All 'reporting possibilities' for Development Substances are classified as confidential in EVMPD. However data export of substance names or codes from EVMPD will be made available in the EudraCT database in line with Article 57 of Regulation (EC) No 726/2004.

See example in Table 17

Table 17. Example of generation of reporting possibilities for development substances

ELEMENTS	REPORTING POSSIBILITIES
Substance EV Code	SUB99999
Current Name/Code	SUB_XYZ_IV [*as Name*]
Previous Names/Codes:	
Previous Name/Code	SUB_XYZ_III [*as Name*]
Previous Name/Code	SUB_XYZ_II_bis [*as Name*]
Previous Name/Code	XYZ [*as Name*]
Previous Name/Code	SUB_XYZ_II [*as Name*]
Previous Name/Code	SUB_XYZ_III [*as Name*]

D.6 Validation of Medicinal Products Reported in ICSRs

The medicinal product information, reported in the data elements *patientdrugname* (ICH E2B(R2) B.1.8a), *parentdrugname* (ICH E2B(R2) B.1.10.8a) or *medicinalproduct* (ICH E2B(R2) B.4.k.2.1), is validated against EVMPD Product Index Database during the Automatic Recoding (See D.1- Validation of Medicinal Products and Active Substances (Automatic recoding)).

The aim of the Automatic Recoding is to associate each reported medicinal product with the corresponding entry in the Product Index Table. This is achieved by retrieving the corresponding Product Index Code in the Product Index Table.

D.6.1 Validation of the Data Elements *patientdrugname* (ICH E2B(R2) B.1.8a) and *parentdrugname* (ICH E2B(R2) B.1.10.8a)

The validation of the data elements *patientdrugname* (ICH E2B(R2) B.1.8a) and *parentdrugname* (ICH E2B(R2) B.1.10.8a) is based on the association of the reported medicinal product with the 'Reporting Possibilities' available in the Product Index Database (See D.4- Product Index Database and 'Reporting Possibilities' for Medicinal Product).

D.6.2 Validation of the Data Element *medicinalproduct* (ICH E2B(R2) B.4.k.2.1)

The data element *medicinalproduct* (ICH E2B(R2) B.4.k.2.1) is validated taking into account the information provided in the other drug related data elements of the ICH E2B(R2) B.4.k section.

These other data elements are:

- *drugauthorizationnumb* (ICH E2B(R2) B.4.k.4.1)
- *drugauthorizationcountry* (ICH E2B(R2) B.4.k.4.2)
- *activesubstancename* (ICH E2B(R2) B.4.k.2.2)
- *drugdosageform* (ICH E2B(R2) B.4.k.7)

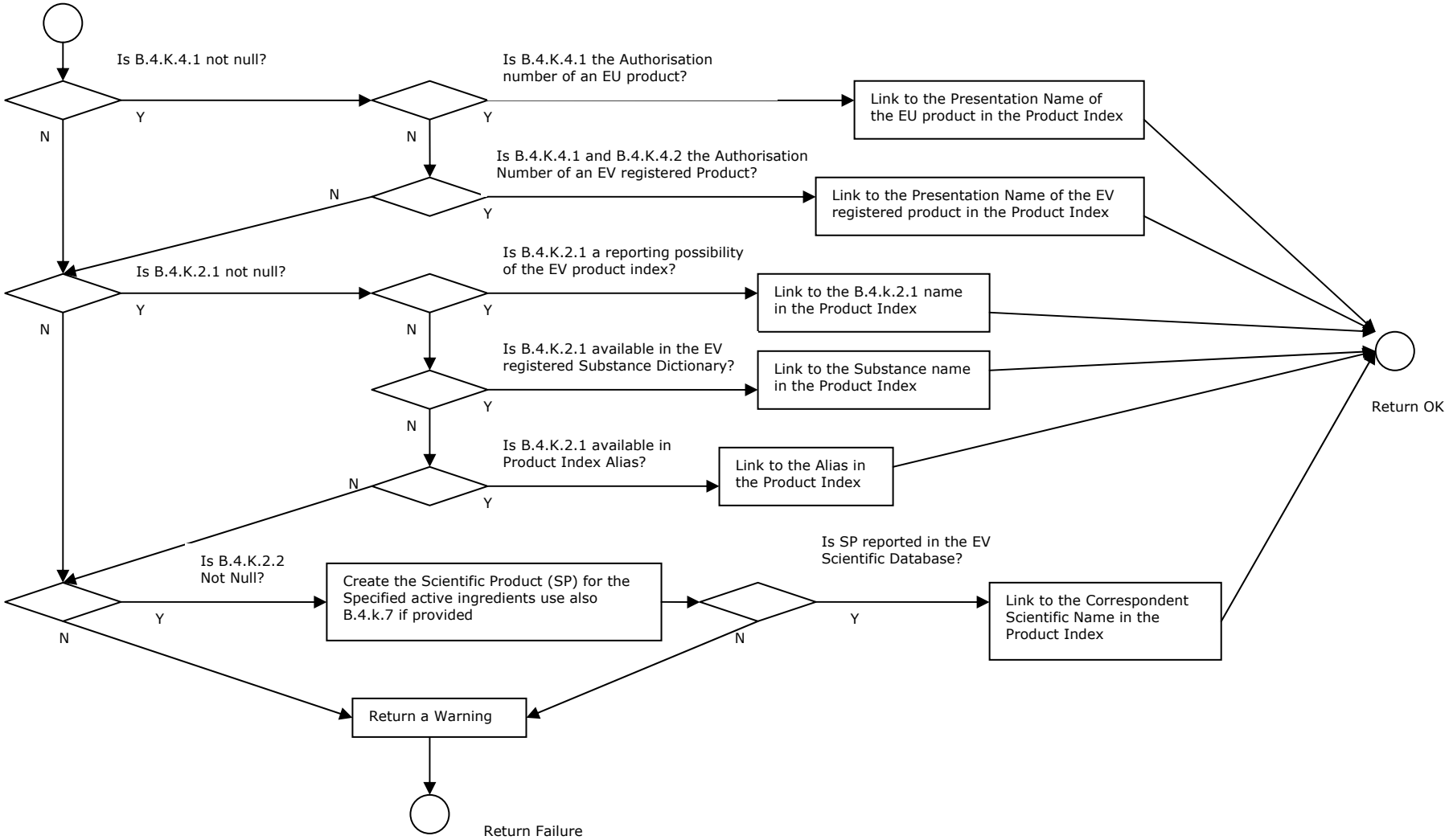
The overall validation of the medicinal products reported in the ICH E2B(R2) B.4.k section is performed in three steps. Each step, if successful, terminates the validation process by retrieving the Product Index Code of the corresponding Product Index entry associated to the medicinal product reported in the ICH E2B(R2) B.4.k section:

1. Validation of the reported medicinal product based on the medicinal product authorisation information provided in the data element *drugauthorizationnumb* (ICH E2B(R2) B.4.k.4.1) and/or *drugauthorizationcountry* (ICH E2B(R2) B.4.k.4.2). This step is not applicable for the development medicinal products.
2. Validation of the medicinal product reported in the data element *medicinalproduct* (ICH E2B(R2) B.4.k.2.1) against the Product Index Database.
3. Validation of the medicinal product based on the active substance(s) reported in the data elements *activesubstancename* (ICH E2B(R2) B.4.k.2.2) and *drugdosageform* (ICH E2B(R2) B.4.k.7).

The algorithm and the three steps followed for the validation of the medicinal product information reported in an ICSR is described in the flowchart provided in Figure 9.

If all three steps fail, the Automatic Recoding of the medicinal product also fails and the Manual Recoding Process is initiated by EMA.

Figure 9. validation of the medicinal product information reported in an ICSR



D.7 Validation of Active Substances Reported in the Data Element activesubstancename (ICH E2B(R2) B.4.k.2.2) of ICSRs

The aim of the Automatic Recoding is to associate the reported active substance with the corresponding entry in EVMPD. This is achieved by retrieving the corresponding active substance EVCODE from EVMPD.

The Automatic Recoding checks the reported active substance against the Product Report Database which includes all approved and development substances entered in EVMPD (See D.5- Product Index Database and 'Reporting Possibilities' for Active Substances).
In case the Automatic Recoding of the active substance fails the Manual Recoding Process is initiated by EMA.

D.8 Reporting of Placebos

If relevant, placebos can be reported in the ICSRs in the following data elements:

- *medicinalproduct* (ICH E2B(R2) B.4.k.2.1)
- *patientdrugname* (ICH E2B(R2) B.1.8a)
- *parentdrugname* (ICH E2B(R2) B.1.10.8a)

Placebos reported in ICSRs are recoded against the entry 'PLACEBO' in the Product Index Database. Placebos do not need to be entered in EVMPD. However, when a placebo is reported in the data element *medicinalproduct* (ICH E2B(R2) B.4.k.2.1) as 'SUSPECT' or 'INTERACTING', the suspected ingredient(s) of the placebo has/have to be specified in the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2).

The possibility to report placebos is applicable to both EVPM and EVCTM.

See Detailed Guidance ENTR/CT 3[18] for the managing of SUSARs associated with placebo.

D.9 Reporting of Blinded Products

If relevant, blinded medication can be reported in ICSRs by using the prefix 'BLINDED' followed by the medicinal product information in one of the following data elements:

- *medicinalproduct* (ICH E2B(R2) B.4.k.2.1)
- *patientdrugname* (ICH E2B(R2) B.1.8a)
- *parentdrugname* (ICH E2B(R2) B.1.10.8a)

The Automatic Recoding is performed based on medicinal product information reported with the prefix 'BLINDED'[19]. The drug section is further flagged as 'BLINDED PRODUCT'.

The possibility to report blinded products is applicable to both EVPM and EVCTM.

Example:

If 'BLINDED XYZ 500 mg' is reported, the medicinal product name is recoded against 'XYZ 500 mg'. In addition the corresponding Drug Section is flagged in the EudraVigilance database as 'BLINDED PRODUCT'.

[18] Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use, Revision 2, April 2006 (ENTR/CT 3)
[19] The search for the prefix 'BLINDED' is case insensitive and should be in capital letters

The recommendations included in the Detailed Guidance ENTR/CT 3 and in the Q&As specific to adverse reactions reporting in clinical trials published in Chapter II of Volume 10 of the Rules Governing Medicinal Products in the European Union should be followed for the reporting of adverse reactions/events in blinded interventional clinical trials.

Appendix E: EudraVigilance Data Security

Once the Safety Messages are sent to EV and loaded into the database they become available for query purposes to EV users.

EV users need to be individually registered with EV in order to be able to access the data, taking into account different levels of access rights to the data stored in EV.

When EV receives a query from a user, security checks are performed, as not all ICSRs are visible to all users. EV has two main policies for data security implemented with regard to access rights.

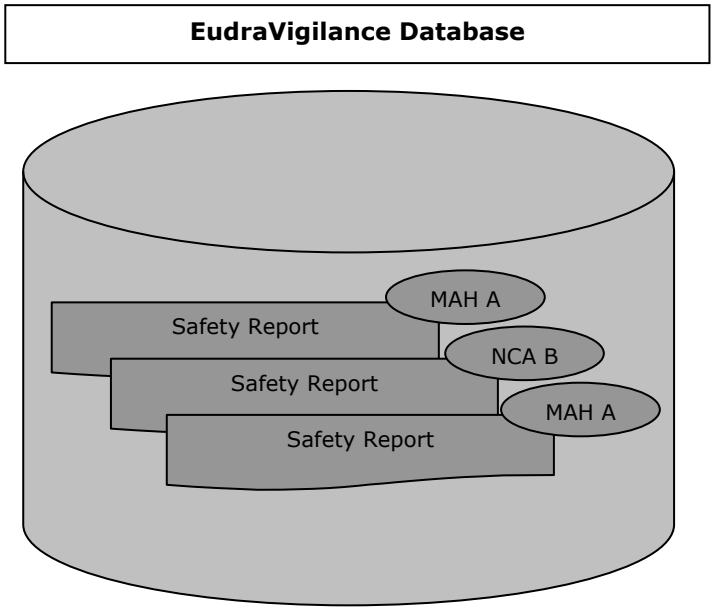
E.1 Sender-Based Security:

This is based on the Message Sender Identifier (ICH M2 M.1.5).

1. A user of a MAH headquarter can only see the ICSRs, that this particular MAH and any registered affiliate organisation associated with the headquarter has submitted to EV.
2. A MAH affiliate organisation can see the ICSRs submitted by them. Additionnly, subject to headquarter approval, the MAH affiliate can see ICSRs submitted by the MAH headquarter.
3. A user belonging to a NCA can see all ICSRs stored in EV, independent of the fact that the ICSRs were submitted by a MAH, Applicant, Sponsor of an interventional clinical trial or of a non-interventional study or another NCA.

The following example reflects the typical behaviour of the sender-based security. EV flags ICSRs with the ownership as displayed in Figure 10. In this example 'A' represents a MAH, 'B' represents a NCA.

Figure 10. Example of ICSRs ownership attributed in EudraVigilance



When a user belonging to the MAH 'A', is accessing EV and is performing a query on the ICSRs stored in EV, the security filter will operate on the ICSRs that were returned as a result of the query. The ICSRs displayed in the report will be only those owned by MAH 'A' as presented in Table 18.

Table 18. ICSRs displayed to user of organisation 'A'

WORLWIDE UNIQUE CASE ID	OWNER
FR-ACME-001	MAH A
FR-ACME-003	MAH A

The data retrieved by the same query, performed by a user belonging to a NCA 'B' are presented in Table 19. In this situation, EV returns all ICSRs that match the query specifications and which are flagged with the ownership of the organisations 'A' and 'B' as NCA users have access to all data.

Table 19. ICSRs displayed to user of organisation 'A'

WORLWIDE UNIQUE CASE ID	OWNER
FR-ACME-001	MAH A
FR-ACME-002	NCA B
FR-ACME-003	MAH A

E.2 Case-Based Security

In EV, MAHs and applicants cannot access other senders' ICSRs even when those ICSRs share the same 'Worldwide unique case identification number' reported in data elements *authoritynumb* (ICH E2B(R2) A.1.10.1) or *companynumb* (ICH E2B(R2) A.1.10.2).

This has been implemented to enhance the EV security taking into consideration the important confidentiality aspects related to the implementation of the EVCT-ICSRs transmissions.

ICSRs sent by different organisations sharing the same 'Worldwide unique case identification number', reported in the data elements *authoritynumb* (ICH E2B(R2) A.1.10.1) or *companynumb* (ICH E2B(R2) A.1.10.2), are grouped together in EV.

The access to the entire set of reports will be granted only to the NCAs, while the access to MAHs or applicants is restricted to the ICSRs they have directly sent to EVPM (sender based security). Sponsors do not have access to any cases submitted to EVCTM.

Currently the system tracks the most recent information about the case with the status = 'Case Report' (See Chapter 10 ICSR Classification).

EV tracks the status = 'Case Report' for each MAH or applicant that sent the ICSRs.

EV tracks also the status = 'Case Report' for the entire set of ICSRs.

NCAs will be able to always see the most updated information for the entire case.

EV sends an alert to the EMA Duplicate Management Administrator if potential duplicates of a case have been detected.

In case there are differences in the content of the ICSRs, the EMA Duplicate Management Administrator will follow up with the senders to determine how best to manage these potential duplicates in EV.

The following example describes the possible scenarios:

A MAH 'A' has sent to EV a Safety Message containing an ICSR. The ICSR stored in EV is marked with the ownership 'A' and is classified with the status = 'Case Report'.

If a new Safety Message arrives in EV from the MAH 'C' and contains an ICSR with the same 'Worldwide unique case identification number', the ICSR is classified again with the status = 'Case Report'.

The system alerts the EMA Duplicate Management Administrator that a potential duplicate has been detected.

The system tracks also the history for the entire set of ICSRs related to the case with the same 'Worldwide unique case identification number'.

Both ICSRs (Case Report and Replaced Report) will be visible when a NCA performs a query in EV (See Table 22).

In the same query, the ICSR with the most recent information sent by the MAH (sender based-security) will be reflected in Tables 20 and 21.

As a consequence, from a user-rights perspective, EV applies the case based security filter as presented in Figure 11.

Table 20. Query result for a user belonging to MAH 'A'

WORLWIDE UNIQUE CASE ID	OWNER	STATUS
FR-ACME-001	MAH A	Case Report

Table 21. Result of same query for a user belonging to MAH 'C'

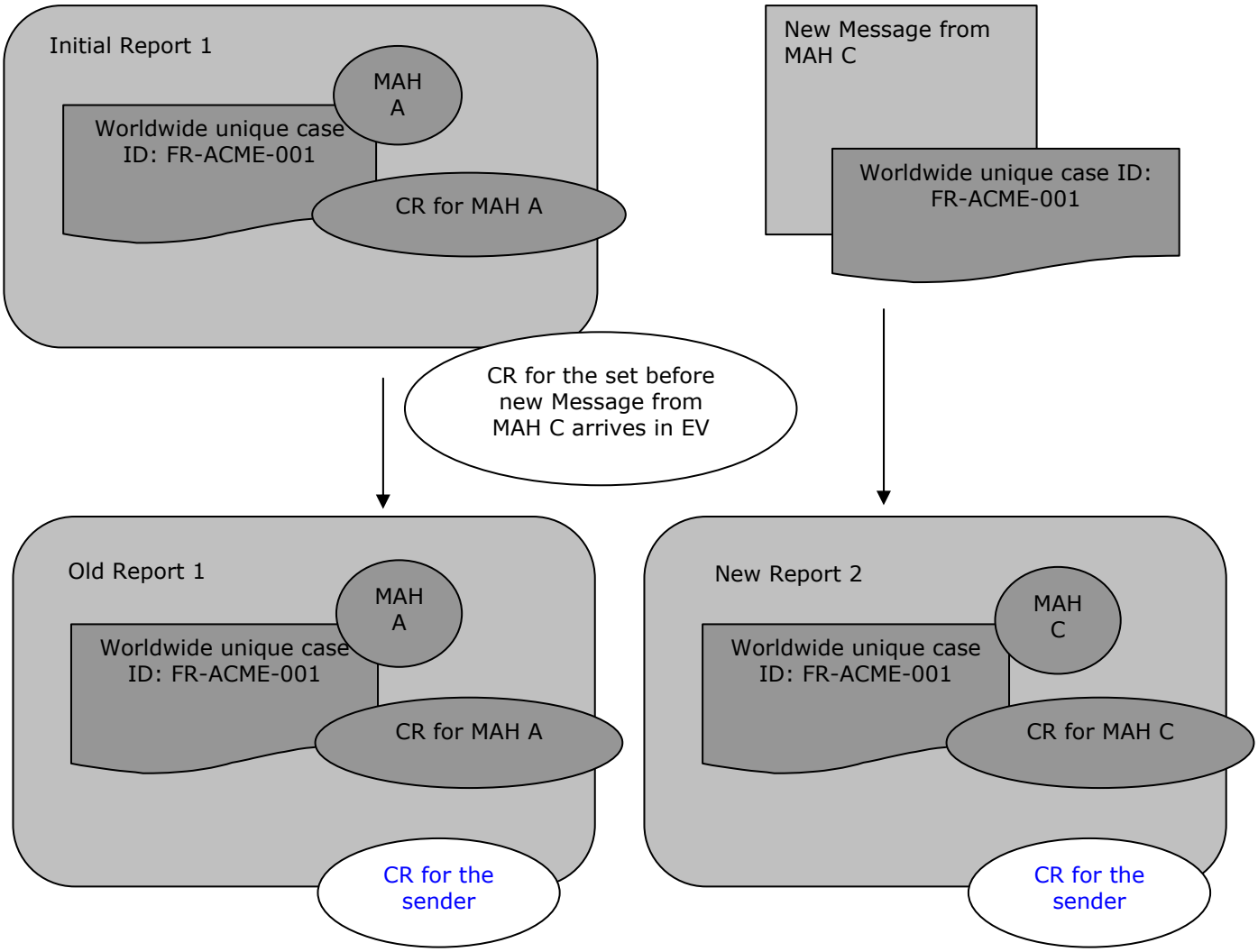
WORLWIDE UNIQUE CASE ID	OWNER	STATUS
FR-ACME-001	MAH C	Case Report

Table 22. Result of same query for a user belonging to a NCA

WORLWIDE UNIQUE CASE ID	OWNER	STATUS
FR-ACME-001	MAH A	Case Report
FR-ACME-001	MAH C	Case Report

Sponsors of interventional clinical trials conducted in the EEA do not currently have access to the ICSRs submitted to EVCTM.

Figure 11. Security filter applied by EudraVigilance (CR= Case Report)



Following duplicate detection management as detailed in Chapter 10.3, a Master Case will be generated referencing these cases. The Master Case will only be visible to EMA and NCAs in EVPM and EVCTM.

Appendix F: Policy on Dosage Form Lookup List

EV uses a lookup list for the data element *drugdosageform* (ICH E2B(R2) B.4.k.7). It is a list of values based on the standard terms of the European Pharmacopoeia. This lookup list is maintained by EMA and new releases are published on the EudraVigilance website: http://eudravigilance.emea.europa.eu/human/PharmaceuticalDoseFormsUpdate.asp (or http://eudravigilance.ema.europa.eu/human/PharmaceuticalDoseFormsUpdate.asp)

The lookup provides information as presented in Table 23.

Table 23. Examples of information provided in the lookup list for the data element *drugdosageform* (ICH E2B(R2) B.4.k.7)

Dosageformcode	**NAME**	***Shortname***	**CLASS**	**STATUS**	**VERSION**
7	Capsule, soft	Capsule	Oral preparations - solid forms		2
25	Cutaneous sponge	Cutaneous sponge	Cutaneous and transdermal preparations	Non current	2
149	Nasal spray, suspension	Nasal spray	Nasal preparations		2
391	Ophthalmic strip	Ophthalmic strip	Eye preparations		3

Table Legend:

***Dosageformcode*:** The EV code of the corresponding dosage form term

Status: The status is 'Non current' when a term is non longer valid in a new release of the European Pharmacopoeia

When a new version of the Dosage Form list is published on the EudraVigilance web site, the following rules apply:

1. The same term never changes its code;
2. A term flagged as non-current in a new release of the Dosage Form list cannot be used in the data element *drugdosageform* (ICH E2B(R2) B.4.k.7) after 3 months from the date when the new version of the Dosage Form list is published on the EudraVigilance website.

Appendix G: Reference to the Previous EudraVigilance User Guidance

This document replaces Note for Guidance EudraVigilance Human – ~~version 7.0~~ Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (Doc. Ref: EMEA/H/20665/04/Final Revision 1).

Appendix H: Specific Local Requirements

Data element *reporterstate* (ICH E2B (R2) A.2.1.2e) and *reporterpostcode* (ICH E2B (R2) A.2.1.2f)

For cases originating in **SPAIN**, at least one of the data elements *reporterstate* (ICH E2B (R2) A.2.1.2e) or *reporterpostcode* (ICH E2B (R2) A.2.1.2f) should be populated in accordance with the following requirements. An error message is generated if none of the data element is populated.

The information provided in the data element *reporterstate* (ICH E2B (R2) A.2.1.2e) should correspond to one of the 19 numeric codes identifying the Autonomous Community where the city/town of the primary source is located. An error message is generated if a valid code is not provided as presented in Table 24

Table 24. Codes identifying the Autonomous Communities in SPAIN

CODES	AUTONOMOUS COMMUNITIES
01	ANDALUCIA
02	ARAGON
03	ASTURIAS
04	ISLAS BALEARES
05	CANARIAS
06	CANTABRIA
07	CASTILLA Y LEON
08	CASTILLA-LA MANCHA
09	CATALUNA
10	COMUNIDAD VALENCIA
11	EXTREMADURA
12	GALICIA
13	COMUNIDAD DE MADRID
14	MURCIA
15	NAVARRA
16	PAIS VASCO
17	LA RIOJA
18	CEUTA
19	MELILLA

The information provided in the data element *reporterpostcode* (ICH E2B (R2) A.2.1.2f) should be the valid 6 digits alphanumeric city/town INE code of the city/town where the primary source is located. An error message is generated if a valid code is not provided.

When both data elements *reporterstate* (ICH E2B (R2) A.2.1.2e) and *reporterpostcode* (ICH E2B (R2) A.2.1.2f) are populated for a primary source, the INE code should match with the Autonomous Community code where the city/town is located. An error message is generated if this validation failed.

Appendix I: Table of Changes

Table 25. Changes applied to this document

DATE	CHANGES APPLIED
April 2003	1. First release of the Technical document for consultation
August 2003	2. The checks on the presence of the fields Reaction Gestation Period and Reaction Gestation Unit has been removed 3. It has been clarified that the *drugrecurrence* [B.4.k.18.1b] field is mandatory within its section. The section *drugrecurrence* [B.4.k.18] is instead optional 4. A check on the fields that require a number and a corresponding measurement unit has been added. When the number is specified the measurement unit should always be present otherwise a warning is generated. The warning will become an error after 30 June 2004. [Appendix B] 5. A check on the field report type has been added and the report type field has become mandatory. A warning will be generated if the report type [A.1.4] field is not filled. The warning will become an error after 30 June 2004 [Appendix B]. 6. The field *drugcumulativedosageunit* [B.4.k.5.7] has been changed from 3 characters to 3 numbers, for consistency with the other measurement unit fields. The previous E2B definition of 3 characters has been interpreted as a typing mistake in the E2B guidance. This change is already in force. 7. A check has been added to the recurrence [B.4.k.17b] field and the *drugreactionasses* [B.4.k.18.1b] field. Values specified in these two fields should be checked against the MedDRA Low Level Terms specified in the reaction section. A warning will be returned until the 30 June 2004 when it will become an error. [Appendix B] 8. It has been clarified that the EudraVigilance system does not check the preferred term that can be specified in the reaction section. [Appendix C Note 7] 9. A policy for the update of the pharmaceutical form [Appendix F] has been defined. 10. An appendix has been added to the technical document providing the list of the changes that have been introduced to the document. [Appendix I]
April 2004	1. Introduction has been updated introducing the reference to the transmission in the two EudraVigilance modules (CT-Module and PM-Module) (Chapter 1). 2. The General ICH Safety Message Flow makes now reference to the EV organisation identifiers used for EVCT and EVPM transmissions (Chapter 5). 3. Appendix A now specifies the business rules applicable for EVCT and EVPM transmissions. 4. Appendix 7 defines the endorsement of the ICH standards in EV7.0, replacing the previous EV6 version. The chapter has been updated with the business rules for EVCTM and EVPM. 5. Appendix E defines the differences between the new version of message

	processing in EV7.0 and the replaced version EV6. The reference to the new business rules for EVPM and EVCTM is also included. 6. Appendix F has been updated in order to include the investigational medicinal products and to describe how the mapping mechanism changes in EV7.0. 7. Appendix G has been updated taking into account the new visibility rules in EV7.0. Reference to the duplicate detection process has been included.
November 2009	1. New mandatory data elements have been added in Appendix A, B and C. Failure to populate these data elements generates an error message: • ICH E2B(R2) A.1.1 *primarysourcecountry*; • ICH E2B(R2) A.1.5.1 serious; • ICH E2B(R2) A.1.5.2 seriousness (for serious reports); • ICH E2B(R2) A.2.1.4 qualification; • ICH E2B(R2) B.2.i.8 *reactionoutcome*; • ICH E2B(R2) B.4.k.1 *drugcharacterisation*; • ICH E2B(R2) B.4.k.2.2 *activesubstancename* for cases submitted to EVCTM when the value in the data element *drugcharacterisation* (ICH E2B(R2) B.4.k.1) is '1' (suspect) or '3' (interacting). • ICH E2B(R2) B.4.k.18 Section Relatedness of Drug to Reaction(s)/Event(s) in relation to suspect/interacting medicinal product(s) for reports submitted to EudraVigilance Clinical Trial Module 2. New validation rules have been added in Appendix A, B and C. <u>a. Failure of the validation generates an error message:</u> • If the data element seriousness (ICH E2B(R2) A.1.5.2) is not empty, the value in the data element serious (ICH E2B(R2) A.1.5.1) should be '1' (Yes). • If ICH E2B(R2) A.1.5.1 serious value is '1' (Yes), at least one ICH E2B(R2) A.1.5.2 seriousness value should be '1' (Yes). • The country code in the first part of the 'Worldwide unique case identification number' reported in the data element *authoritynumb* (ICH E2B(R2) A.1.10.1) and *companynumb* (ICH E2B(R2) A.1.10.2) should be a valid ISO3166 country code. • All reported country names should be valid ISO3166 country codes except in section 'Narrative case summary and further information' (ICH E2B B.5). • If populated, Patient's and/or parent's age should be < 150 years; Patient's and/or parent's weight should be < 650 kg; Patient's and/or parent's height should be < 250 cm. • For ICSRs submitted to EVPM, if the value in the data element *reactionoutcome* (ICH E2B(R2) B.2.i.8) is '5' (Fatal) for at least one reaction then the value in the data element *serious* (ICH E2B(R2) A.1.5.1) should be '1' (Yes) and the value in the data element *seriousnessdeath* (ICH E2B(R2) A.1.5.2) should be '1' (Yes) • For ICSRs submitted to EVPM and EVCTM, if the value in the data element *serious* (ICH E2B(R2) A.1.5.1) is '1' (Yes) and the value in the data element *seriousnessdeath* (ICH E2B(R2) A.1.5.2) is '1' (Yes), then the value in the data element *reactionoutcome* (ICH E2B(R2) B.2.i.8) should be '5' (Fatal) for at least one reaction. • At least one of the reported drug should have the corresponding data

element *drugcharacterisation* (ICH E2B(R2) B.4.k.1) populated with the value '1' (Suspect) or '3' (Interacting).

- For cases submitted to EVCTM, the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) should be populated when the value in the data element *drugcharacterisation* (ICH E2B(R2) B.4.k.1) is '1' (suspect) or '3' (interacting).
- All dates (including imprecise dates) should not be in the future.
- All reported dates should be inferior or equal to the EudraVigilance Gateway date ~~reported in the data element *receiptdate* (ICH E2B(R2) A.1.7b) except for the data element *messagedate* (ICH M2 M.1.7b) and *transmissiondate* (ICH E2B(R2) A.1.3b)~~.
- All start dates should be inferior or equal to their corresponding end dates.
- For any transmission to EVCTM,
  - The data element *studyname* (ICH E2B(R2) A.2.3.1) should contain:
    a) For SUSARs originating in the EEA:
    - 'Valid EudraCT Number#Study abbreviated name',
    when the values in the data element *primarysourcecountry* (ICH E2B(R2) A.1.1) and *occurcountry* (ICH E2B(R2) A.1.2) are EEA countries.
    b) For SUSARs originating outside the EEA:
    - 'Valid EudraCT Number#Study abbreviated name' or
    - '#Study abbreviated name',
    when the values in the data element *primarysourcecountry* (ICH E2B(R2) A.1.1) and *occurcountry* (ICH E2B(R2) A.1.2) are non-EEA countries.
  - The section Relatedness of Drug to Reaction(s)/Event(s) (ICH E2B(R2) B.4.k.18) in relation to suspect/interacting medicinal product(s) should be populated for any reported event/reaction.
  - Any initial ICSR should contain at least one reaction with a causality assessment 'Reasonable possibility' to at least one of the reported medicinal products classified as suspect or interacting. This rule is not applied to follow-up ICSR in order to leave sponsors the possibility to downgrade the causality of an initial ICSR.
- For ICSRs sent to EVPM, when the value of the data element *reporttype* (ICH E2B(R2) A.1.4) is '2' (report from study), the data element *observestudytype* (ICH E2B(R2) A.2.3.3) should not be NULL and the accepted value is '2' (individual patient use) or '3' (other studies). When the value of the data element *observestudytype* (ICH E2B(R2) A.2.3.3) is '2' (individual patient use) or '3' (other studies), the accepted value for the data element *reporttype* (ICH E2B(R2) A.1.4) is '2' (report from study).
- When populated the data element *testname* (ICH E2B(R2) B.3.1c) should contain a valid LLT MedDRA name or code.
- Only numeric MedDRA LLT codes should be used in designated fields (except in the data element *testname* (ICH E2B(R2) B.3.1c) where valid MedDRA LLT names are also accepted).
- No follow-up report can be submitted for cases which have been previously nullified. When an ICSR contains the value '1' (yes) in the data element *casenullification* (ICH E2B(R2) A.1.13), an error message will be generated for any additional follow-up report submitted for this case. A new case, with

	a different 'Worldwide unique case identification number' in the data element *authoritynumb* (ICH E2B(R2) A.1.10.1) or *companynumb* (ICH E2B(R2) A.1.10.2), should be created and submitted if necessary. b. Failure of the validation generates an warning message: • For cases submitted to EVPM, the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) should be populated if the value in data element *drugcharacterisation* (ICH E2B(R2) B.4.k.1) is '1' (suspect) or '3' (interacting). • If the data element *drugdosageform* (ICH E2B(R2) B.4.k.7) is not null, the failure of a successful match with the latest version of the European Pharmacopoeia Dosage Forms list generates a warning. 3. Information on the validation procedures of the medicinal products and active substances reported in ICSRs has been updated and rules for reporting placebos and blinded products (if relevant) have been added (Appendix D).
October 2010	1. New mandatory data elements have been added in Appendix A and C. Failure to populate these data elements generates an error message: • ICH E2B(R2) B.4.k.18 Section Relatedness of Drug to Reaction(s)/Event(s) in relation to suspect/interacting medicinal product(s) for reports submitted to EudraVigilance Clinical Trial Module 2. New validation rules have been added in Appendix A and C. a. Failure of the validation generates an error message: • For ICSRs submitted to EVPM and EVCTM, if the value in the data element *serious* (ICH E2B(R2) A.1.5.1) is '1' (Yes) and the value in the data element *seriousnessdeath* (ICH E2B(R2) A.1.5.2) is '1' (Yes), then the value in the data element *reactionoutcome* (ICH E2B(R2) B.2.i.8) should be '5' (Fatal) for at least one reaction. • All reported dates should be inferior or equal to the EudraVigilance Gateway date. • For any transmission to EVCTM, - The section Relatedness of Drug to Reaction(s)/Event(s) (ICH E2B(R2) B.4.k.18) in relation to suspect/interacting medicinal product(s) should be populated for any reported event/reaction. - Any initial ICSR should contain at least one reaction with a causality assessment 'Reasonable possibility' to at least one of the reported medicinal products classified as suspect or interacting. This rule is not applied to follow-up ICSR in order to leave sponsors the possibility to downgrade the causality of an initial ICSR.

Appendix J: Terms in relation to electronic exchange of safety information

Acknowledgement Message for ICSR (ICSRACK)

An Electronic Data Interchange (EDI) Message with the information on the result of the Acknowledgement of Receipt procedure to acknowledge the receipt of one Safety Message and the ICSR(s) contained in the Safety File.

Acknowledgement Message for Medicinal Product (MPRACK)

An EDI Message with the information on the result of the Acknowledgement of Receipt procedure to acknowledge the receipt of one Medicinal Product Report Message and the Medicinal Product Report(s) contained in the Medicinal Product File.

Acknowledgement of Receipt

An acknowledgment of receipt is a message created and returned to the sender organisation, recognising that a message has been received.

Applicant

A pharmaceutical company applying for a marketing authorisation in the EEA.

Approved Substance

Any substance as defined in Directive 2001/83/EC as amended, which is an ingredient of a medicinal product for which a marketing authorisation was granted within or outside the EEA.

Authorised Medicinal Product (AMP)

A medicinal product authorised by a Regulatory Authority either within the EEA or outside the EEA.

Development Medicinal Product (DMP)

A medicinal product, under investigation in an interventional clinical trial, which does not have a marketing authorisation in the EEA and to which special confidentiality arrangements may need to be applied.

Development Substance

Any substance under investigation in an interventional clinical trial and which is not contained in any Authorised Medicinal Product (AMP).

Electronic Data Interchange (EDI)

Electronic transfer, from computer to computer, of commercial and administrative data using an agreed standard to structure an EDI message. EDI is based on the use of structured and coded messages, the main characteristic of which is their ability to be processed by computers and transmitted automatically and without ambiguity. This makes EDI specific in comparison with other data exchange such as electronic mail.

EudraVigilance Database Management System (EVDBMS)

It is the core element of the European pharmacovigilance database defined in EU legislation.

EudraVigilance Data Warehouse and Analysis System (EVDAS)

The EudraVigilance Data warehouse Analysis System has been designed to allow users to analyse safety data collected in EudraVigilance in view of allowing better-informed decisions about the safety profile of medicinal products. It provides a range of analytical tools: from measuring reporting compliance for regulatory purposes, to pharmacovigilance analyses (such as signal detection tools).

EudraVigilance Gateway

The data-processing network as defined in the EU legislation that provides a single point of contact between MAHs, Applicants, Sponsors of interventional clinical trials and non-interventional studies, NCAs in the EEA and EMA. By doing so, the EudraVigilance Gateway is considered a hub and all connections to the EDI Partners are known as spokes. Safety, Acknowledgement and Medicinal Product Report Messages are routed through the hub to the desired spoke.

Extensible Markup Language (XML)

A subset of SGML that is completely compatible with SGML.

EudraVigilance Medicinal Product Dictionary (EVMPD)

The EVMPD has been developed to assist the pharmacovigilance activities in the European Economic Area. It has been designed to support the collection, reporting, coding and evaluation of authorised and investigational medicinal product data in a standardised and structured way. It is used as standard dictionary to support the coding of medicinal products and active substances described in individual case safety reports submitted to EudraVigilance.

Electronic Standards for the Transmission of Regulatory Information (ESTRI)

Definition of standards that enable the electronic transfer of regulatory information

EudraVigilance Web Trader

A web tool that is made available by EMA to interested registered parties, providing a way to exchange Safety and Acknowledgment Messages in a semiautomatic way using the EudraVigilance web application, EVWEB.

Gateway

A data exchange service, which consists of all core standards and functionality required for supporting the ICH standards (e.g. Simple Mail Transfer Protocol (SMTP)/Secure Multipurpose Internet Mail (SMIME)).

Individual case

The information provided by a primary source to describe suspected adverse reactions/suspected unexpected serious adverse reactions related to the administration of one or more medicinal products/investigational medicinal products to an individual patient at a particular point of time.

Individual Case Safety Report (ICSR)

An Individual Case Safety Report is a document providing the most complete information related to an Individual Case at a certain point of time. An ICSR may also be referred to as Safety Report.

Investigational medicinal product (IMP)

A pharmaceutical form of an active substance or placebo being tested or used as a reference in an interventional clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an

unauthorised indication, or when used to gain further information about the authorised form (Art 1(d) of Directive 2001/20/EC).

Medicinal Product (MP)

Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances, which may be used in or administered to human beings either with the view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to make a medical diagnosis (Directive 2001/83/EC as amended).

Medicinal Product File

The electronic file transmitted in one Message Transaction between one Sender and one Receiver containing one Medicinal Product Report Message.

Medicinal Product Report (MPR)

An electronic report with a defined set of data elements to populate and update the EudraVigilance Medicinal Product Dictionary. A Medicinal Product Report may contain information on an authorised medicinal product/investigational medicinal product.

Medicinal Product Report Message (MPRM)

An EDI Message including the information provided for one/more Medicinal Product Reports contained in one Medicinal Product File exchanged between one Sender and one Receiver in one Message Transaction.

Message

An EDI Message consists of a set of segments structured using an agreed standard, prepared in a computer readable format and capable of being automatically and unambiguously processed.

Message Disposition Notification (MDN)

A notification on the receipt of an EDI Message returned by the Receiver's Gateway to the Sender's Gateway. The MDN concludes a Message Transaction performed between two parties in a Gateway to Gateway communication.

Message Transaction

A set of actions encompassing the electronic transmission of an EDI Message (Safety Message, Acknowledgement Message, Medicinal Product Message) between a Sender and a Receiver including the return of the Message Disposition Notification for that message.

Partner

An organisation exchanging EDI Messages in the area of pharmacovigilance in the pre- or post-authorisation phase with another organisation. For the purpose of this guideline, EDI partners in the pre- and post-authorisation phase in pharmacovigilance are as follows:

- NCAs in the EEA
- EMA
- MAHs in the EEA
- Applicants
- Sponsors of interventional clinical trials and non-interventional studies in the EEA

Pharmaceutical Product

A medicinal product may consist of one or several pharmaceutical products, which are characterised through one or more active substances, the strength of the substances, the pharmaceutical form and one or more routes of administration.

Receiver

Intended recipient of the EDI Message.

Receiver Identifier

Identification or combined EDI qualifier and ID of the recipient.

Report Receiver

Intended recipient of the transmission of a Safety Message, which for the purpose of this Guideline is an EDI Partner. The Receiver is also the intended recipient of the transmission of a Medicinal Product Report Message, who for the purpose of this Guideline is EMA.

Report Sender

Person or entity creating a Safety Message as EDI Message in order to submit an ICSR, which for the purpose of this Guideline is an EDI Partner being an Applicant, a MAH or a Sponsor of an interventional clinical trial or of a non-interventional study. In the Report Transaction the Report Sender will always remain the same, whereas with the exchange of messages the "Sender" and "Receiver" roles will change. The same concepts apply to the organisation creating a Medicinal Product Message as EDI Message in order to submit a Medicinal Product Report, which for the purpose of this Guideline is an EDI Partner being an Applicant, a MAH or a Sponsor of an interventional clinical trial.

Safety File

The electronic file transmitted in one Message Transaction between one Sender and one Receiver containing one Safety Message.

Safety Message

An EDI Message including the information provided for one/more ICSR(s) contained in one Safety File exchanged between one Sender and one Receiver in one Message Transaction.

Sender

Person or entity creating an EDI Message for transmission.

Sender Identifier

Identification (ID) or combined EDI qualifier and ID of the Sender.

Standard Generalised Markup Language (SGML)

International Standard (ISO 8879) computer language for describing a document in terms of its content (text, image) and logical structure (chapters, paragraphs, etc.). It is a standard for how to specify a document markup language or tag set. Such a specification is itself a document type definition (DTD). SGML is not in itself a document language, but a description of how to specify one. It is a metalanguage. SGML is based on the idea that documents have structural and other semantic elements that can be described without reference to how such elements should be displayed.