European Medicines Agency
*Post-authorisation Evaluation of Medicines for Human Use*

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# NOTE FOR GUIDANCE

# EUDRAVIGILANCE HUMAN VERSION 7.1

# PROCESSING OF SAFETY MESSAGES AND INDIVIDUAL CASE SAFETY REPORTS (ICSRS)

| | |
|---|---|
| **DISCUSSION AT EUDRAVIGILANCE EXPERT WORKING GROUP (EV-EWG)** | Feb 2007 |
| **DISCUSSION AT CHMP PHARMACOVIGILANCE WORKING PARTY (PhVWP)** | May 2007 |
| **DISCUSSION AT EUDRAVIGILANCE TELEMATICS IMPLEMENTATION GROUP (EVTIG)** | Sep 2007 |
| **DISCUSSION AT EUDRAVIGILANCE STEERING COMMITTEE** | Oct 2007 |
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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 Version 7.0 – Processing of Safety Messages and Individual Case Safety Reports (ICSRs)' (Doc. Ref. EMEA/H/20665/04/Final).

The following aspects are outlined in detail:

- The data quality principles of ISCRs transmitted electronically
- The generation of a valid ICH Safety Message
- The requirements for the correct loading of ICH Safety Messages in EV7.1
- The General ICH Safety Message Flow
- The ICH Safety Message Flow in EV7.1
- The Safety Messages and ICSRs
- The ICH Acknowledgement Message
- The ICSR Classification
- The description of the mandatory ICH E2B(R2) data elements and of the complete list of validation checks performed by EV7.1
- The concepts of the lookups for the medicinal product information validation and the rules for reporting placebos and blinded products
- The EudraVigilance data security

Based on the experience gained since the release of EV7.0, new validation rules including mandatory ICH E2B(R2) data elements are being applied when ICSRs are transmitted to EV. 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: Pharmacovigilance for medicinal products for human use.

| | |
|---|---|
| New mandatory ICH E2B(R2) data elements generating error messages | • Identification of the country of the primary source<br>• Seriousness (yes/no)<br>• Seriousness criteria<br>• Was the case medically confirmed if not initially from a health professional, for INITIAL non-health professional reports<br>• Outcome of reaction/event at the time of the last observation<br>• Characterisation of drug role<br>• Active substance name(s), when drug is suspect or interacting |
| New validation rules generating error messages | • Seriousness criteria should match with the ICSR Seriousness<br>• All reported country names, including the first part of the 'Worldwide unique case identification number', should be valid ISO3166 country codes<br>• Values of age, weight and height should not be above 150 years, 650 Kg and 250 cm respectively<br>• For spontaneous reports and reports originating from non-interventional trial, at least one reaction should have a fatal outcome if the ICSR is serious and with a seriousness criteria 'Results in death' |

| | |
|---|---|
| | • At least one drug in the report should be 'suspect' or 'interacting'<br>• All dates (including imprecise dates) should not be in the future<br>• All start dates should be inferior or equal to their corresponding end dates<br>• 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<br>• For any transmission to the EudraVigilance Clinical Trial Module, the 'Study name' data element should contain:<br>a) For SUSARs originating in the EEA:<br>- 'Valid EudraCT Number#Study name',<br>b) For SUSARs originating outside the EEA:<br>- 'Valid EudraCT Number#Study name' or 'Valid Development Medicinal Product EV Code#Study name'<br>• Any report from study transmitted to the EudraVigilance Post Authorisation Module, should have the data element 'Study type' populated with 'individual patient use' or 'other studies' |

The new validation rules and mandatory ICH E2B(R2) data elements will be applicable when the new EudraVigilance version 7.1 (EV7.1) message processing part enters into force.

**The business rules as outlined in this guidance are applicable to all stakeholders, which are exchanging Safety Messages and ICSRs electronically at Community level in line with Regulation (EC) No 726/2004, Directive 2001/83/EC as amended, Directive 2001/20/EC, Volume 9A and Volume 10 (Clinical Trials, Chapter II : Monitoring and Pharmacovigilance).**

## TABLE OF CONTENT

# 1 Introduction

This guidance describes the aspects of the message processing and acknowledgment generation implemented in EudraVigilance (EV[1]).

It updates and replaces the business rules and validations as described in the '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).

This guidance is applicable to all stakeholders, which are exchanging Safety Messages and ICSRs electronically at Community level in line with Regulation (EC) No 726/2004, Directive 2001/83/EC as amended, Directive 2001/20/EC, Volume 9A and Volume 10 (Clinical Trials, Chapter II : Monitoring and Pharmacovigilance).

Based on the experience gained since the release of EV7.0, new validation rules and mandatory ICH E2B(R2)[2] data elements are to be applied when the ICSRs[3] transmitted to EudraVigilance are processed. 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: Pharmacovigilance for medicinal products for human use.

The new validation rules and mandatory ICH E2B(R2) data elements will be applicable when the new EudraVigilance version 7.1 (EV7.1) message processing part enters into force.

Taking into account the implementation of the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) in the frame of Directive 2001/20/EC, EudraVigilance includes two reporting modules:

1. **EudraVigilance Post-Marketing Module (EVPM):** related to ICSRs that need to be reported according to Regulation (EC) No. 726/2004, Directive 2004/27/EC and taking into account Volume 9A. The Safety Messages sent to this module contain spontaneous reports and reports from non-interventional trials only. 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. **EudraVigilance Clinical Trial Module (EVCTM):** related to ICSRs that need to be reported in accordance with Directive 2001/20/EC and Volume 10. The Safety Messages sent to this module contain reports from interventional clinical trials only. The ICSRs received in this module will be referred to in this document as EVCT-ICSRs (EudraVigilance Clinical Trial Individual Case Safety Reports).

The following aspects are outlined in detail in this document:

- The data quality principles of ISCRs transmitted electronically (Chapter 2)
- The generation of a valid ICH Safety Message (Chapter 3)
- The requirements for the correct loading of ICH Safety Messages in EV7.1 (Chapter 4)
- The General ICH Safety Message Flow (Chapter 5)

[1] EudraVigilance will be referred to as "EV" in the document for all aspects not depending on a particular version or release. Otherwise EudraVigilance will be referred to as "EVX" or "EVX.Y" where X.Y stands for a specific version and release.

[2] **E2B(R2) is the new reference for the ICH guideline E2B(M)**. See http://www.ich.org/LOB/media/MEDIA2217.pdf

[3] When the transmission of Safety Reports is quoted as "ICSRs" it refers to both EVPM-ICSRs and to EVCT-ICSRs.

- The ICH Safety Message Flow in EV7.1 (Chapter 6)
- The Safety Messages and ICSRs (Chapter 7)
- The ICH Acknowledgement Message (Chapter 8)
- The ICSR Classification (Chapter 9)

The document describes which aspects refer specifically to the EVPM-ICSR transmissions or the EVCT-ICSR transmissions 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 EV7.1 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 Pharmaceutical Form Lookup List is described in Appendix F.
- The reference to the EudraVigilance User Guidance is provided in Appendix G.
- A table of changes is presented in Appendix H.
- The definitions of the terms in relation to the electronic exchange of safety information are available in Appendix I.

## 2 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 EudraVigilance in line with Regulation (EC) No 726/2004, Directive 2001/83/EC as amended, Directive 2001/20/EC, Volume 9A and Volume 10 (Clinical Trials, Chapter II: Monitoring and Pharmacovigilance).

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 on request.

# 3 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 'Electronic Transmission of Individual Case Safety Report Message Specification version 2.3 (ICH ICSR DTD Version 2.1)'. This is a prerequisite for each party to successfully exchange Safety Messages with EV.

## 3.1 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.

In the Electronic Transmission of Individual Case Safety Reports Message Specification (ICH ICSR DTD Version 2.1), Final Version 2.3, Document Revision February 1, 2001, it is specified that a method of labeling the tags with a language attribute is used, which is widely accepted also in XML.

A valid XML Safety or Acknowledgment Message needs to include an XML header and a Document Type Definition (DTD) reference. In this context, the character set used for the Safety and Acknowledgement Messages should also be declared. The accepted character sets are for Safety Messages LATIN-1 (ISO-8859-1) and UNICODE (UTF-8; UTF-16). The Acknowledgement Messages are returned by EV7.1 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://ers.emea.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://ers.emea.europa.eu/dtd/ichicsrack11xml.dtd">*

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]

In addition, as XML is case sensitive, all the field and attribute 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 conforms 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 >, < 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/.

# 4 Requirements for the Correct Loading of ICH Safety Messages in EV7.1

This chapter defines the rules that should be followed to be able to exchange Safety Messages with EV7.1 successfully. Appendixes (A-C) describe these rules in detail.

A Safety Message, to be successfully loaded in EV7.1, should conform to the Safety Message standards (ICH DTD) and should respect the business rules defined in Appendix A to C.

# 5 The General ICH Safety Message Flow

This chapter describes the Safety Message exchange with EV7.1 between all relevant parties involved in safety monitoring in the EEA. In order to transport 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 the EMEA, i.e., only those parties that are registered with the EMEA are able to exchange Safety Messages either with the EMEA (EV7.1) or other registered parties (EudraVigilance community).

The list of all possible parties refers to National Competent Authorities (NCAs), Marketing Authorisation Holders (MAHs), Applicants for a marketing authorisation and Sponsors of Clinical Trials.

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 the EMEA 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 possible communication scenarios are the following:

**Reporting to EudraVigilance** (EVPM and EVCTM):

a. NCAs, MAHs, Applicants and Sponsors of Clinical Trials send Safety Messages to the EMEA. They can submit ICSRs to the EVPM-Module and to the EVCT-Module.

**Re-routing via EudraVigilance**:

a. MAHs, Applicants and Sponsors of Clinical Trials send Safety and Acknowledgment Messages to NCAs in the EEA;
b. NCAs send Safety and Acknowledgments Messages to MAHs, Applicants and Sponsors of Clinical Trials.

### 5.1 Reporting to the EVPM-Module (Figure 1):

1. A NCA, MAH, Applicant or Sponsor of a Clinical Trial sends ICSR(s) in a Safety Message to EV7.1.
2. The Safety Message is delivered to the EV test environment or the EV production environment of the EVPM-Module if the receiver identifier specified in the Safety Message is EVTEST or EVHUMAN respectively;
3. EV7.1 sends an Acknowledgement Message (ACK) to confirm the receipt of the Safety Message and of the ICSR(s);

The example below (Figure 1) reflects the exchange of a Safety Message including one or several ICSRs from a MAH to EV7.1 and from a NCA to EV 7.1.

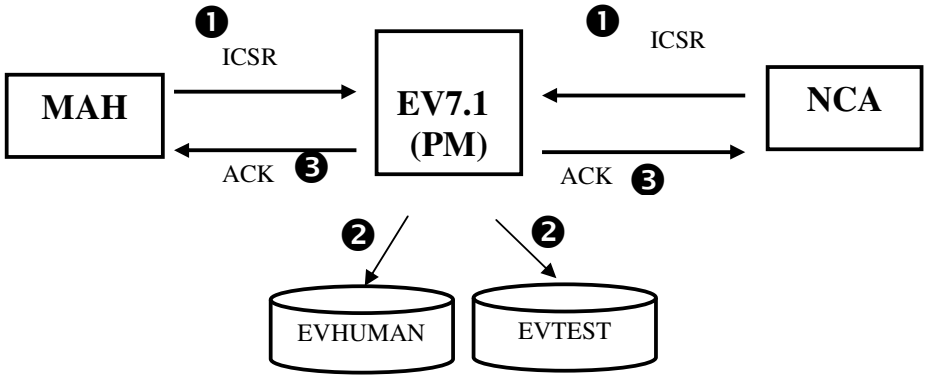


Figure 1

### 5.2 Reporting to the EVCT-Module (Figure 2):

1. A NCA, or Sponsor of a Clinical Trial sends ICSR(s) in a Safety Message to EV7.1.
2. The Safety Message is delivered to the EV test environment or to the EV production environment of the EVCT-Module if the receiver identifier specified in the Safety Message is EVCTMTEST or EVCTMPROD respectively;
3. EV7.1 sends an Acknowledgement Message (ACK) to confirm the receipt of the Safety Message and of the ICSR(s);

The example (Figure 2) reflects the exchange of a Safety Message including one or several ICSRs from a Sponsor to EV7.1 and from a NCA to EV 7.1.

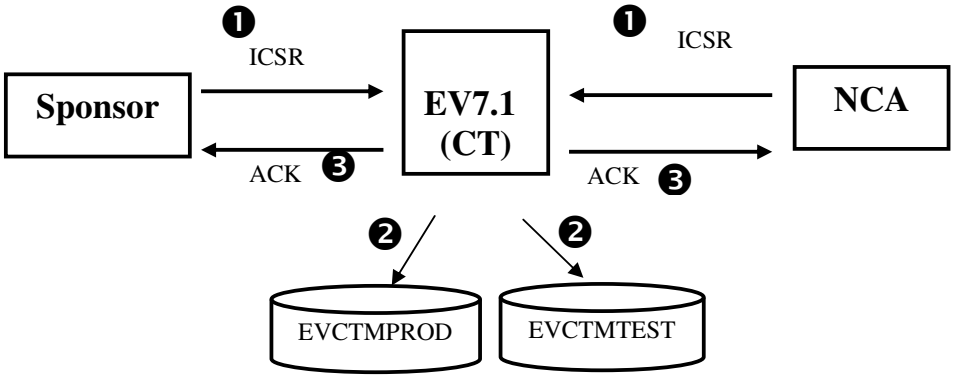

Figure 2

**5.3 Re-routing via EV7.1:**

a) A MAH, Applicant or Sponsor of a Clinical Trial sends a Safety Message to a NCA in the EEA (Figure 3):

1. A MAH, Applicant or Sponsor of a Clinical Trial sends ICSR(s) included in a Safety Message via EV7.1 to a NCA;
2. A NCA sends an Acknowledgement Message (ACK) via EV7.1 to confirm the receipt of the Safety Message and of ICSR(s);

The example (Figure 3) reflects the exchange of a Safety Message including one or several ICSRs from a MAH/Sponsor to a NCA via EV 7.1.

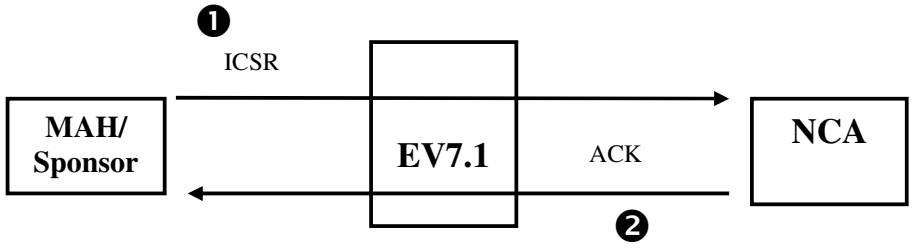


Figure 3

b) A NCA in the EEA sends a Safety Messages to a MAH, Applicant or Sponsor of a Clinical Trial (Figure 4):

1. A NCA sends ICSR(s) in a Safety Message via EV7.1 to a MAH, Applicant or Sponsor of a Clinical Trial;
2. The MAH, Applicant or Sponsor of a Clinical Trial sends an Acknowledgement Message (ACK) via EV7.1 to confirm the receipt of the Safety Message and of ICSR(s);

The example (Figure 4) below reflects the exchange of a Safety Message including one or several ICSRs from a NCA to a MAH/Sponsor via EV 7.1.

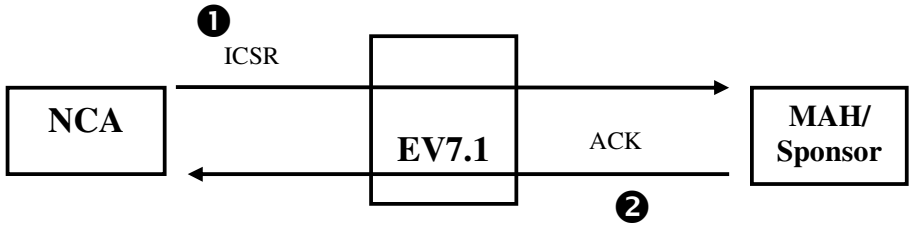


Figure 4

# 6 The ICH Safety Message Flow in EV7.1

This chapter describes the Safety Message flow in EV7.1 and outlines when an Acknowledgment Message is generated and when it is not generated (Figure 5). The later may be the case, if e.g. the Safety Message is not well-formed and/or valid (Refer to chapter 3 for generating a valid Safety Message).

EV7.1 performs a validation of any incoming Safety Message in two steps:

## 6.1 Inbound Parsing Validation:

EV7.1 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 3. In case the sender has not included the correct DTD reference header as indicated in chapter 3, the return of an Acknowledgment Message cannot be guaranteed by the receiver.

In case of the detection of a parsing error by EV7.1, the following scenarios may occur:

- If during the parsing process of the Safety Message, EV7.1 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, EV7.1 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 EV7.1 cannot recognize the receiver identifier because the receiver is not registered with the EMEA, 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.

In case the Safety Message is valid according the Safety Message DTD validation, EV7.1 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 EV7.1 will return a Transmission Acknowledgement Code '03' i.e., no data extracted.
- Upload the Safety Message with the Inbound Load Process into EV7.1 database.

## 6.2 Inbound Loading Process into EV7.1

The processing of the 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 to be processed and uploaded:

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

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

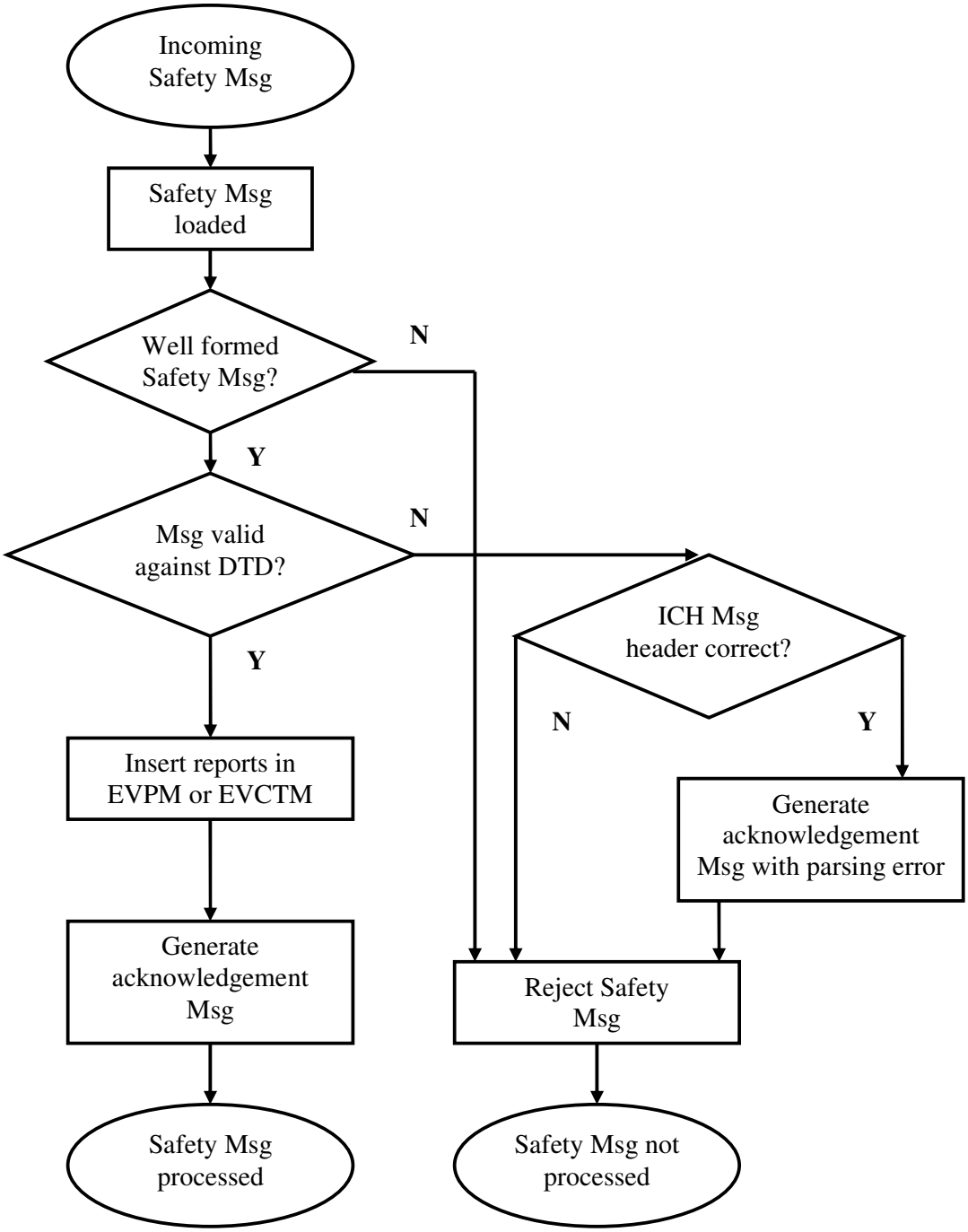


Figure 5: Safety Message (Msg) flow

# 7 ICH Safety Messages and Individual Case Safety Reports (ICSRs)

This chapter introduces the concepts of a Safety Message and Individual Case Safety Reports (ICSRs), also referred to as Safety Reports.

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 3.

## 7.1 Message Header

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

### *7.1.1 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 ICH M2 document 'Electronic Transmission of Individual Case Safety Report Message Specification version 2.3 (ICH ICSR DTD Version 2.1)'. When creating an Safety Message, the value of this field should be 'ichicsr'.

### *7.1.2 Message Format Version*

The data element *messageformatversion* (ICH M2 M.1.2) contains the version number of the DTD and it is specified in the ICH M2 document 'Electronic Transmission of Individual Case Safety Report Message Specification version 2.3 (ICH ICSR DTD Version 2.1)'. The acceptable message format version number is 2.1.

### *7.1.3 Message Format Release*

The data element *messageformatrelease* (ICH M2 M.1.3) specifies the release number of the message format version number of the DTD. The acceptable message format release numbers are 1.0 and the 2.0.

### *7.1.4 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.

### *7.1.5 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 the EMEA.

### *7.1.6 Message Receiver Identifier*

The data element *messagerecieveridentifier* (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 in the registration process with the EMEA.

### *7.1.7 Message Date and Format*

The data element *messagedate* (ICH M2 M.1.7b) provides information on which the Safety Message was initiated. The default value for the data element *messagedateformat* (ICH M2 M.1.7a) is '204' i.e., CCYYMMDDHHMMSS.

The following diagram (Figure 6) illustrates the relationship between a Safety Message and one or more ICSRs attached to this message.

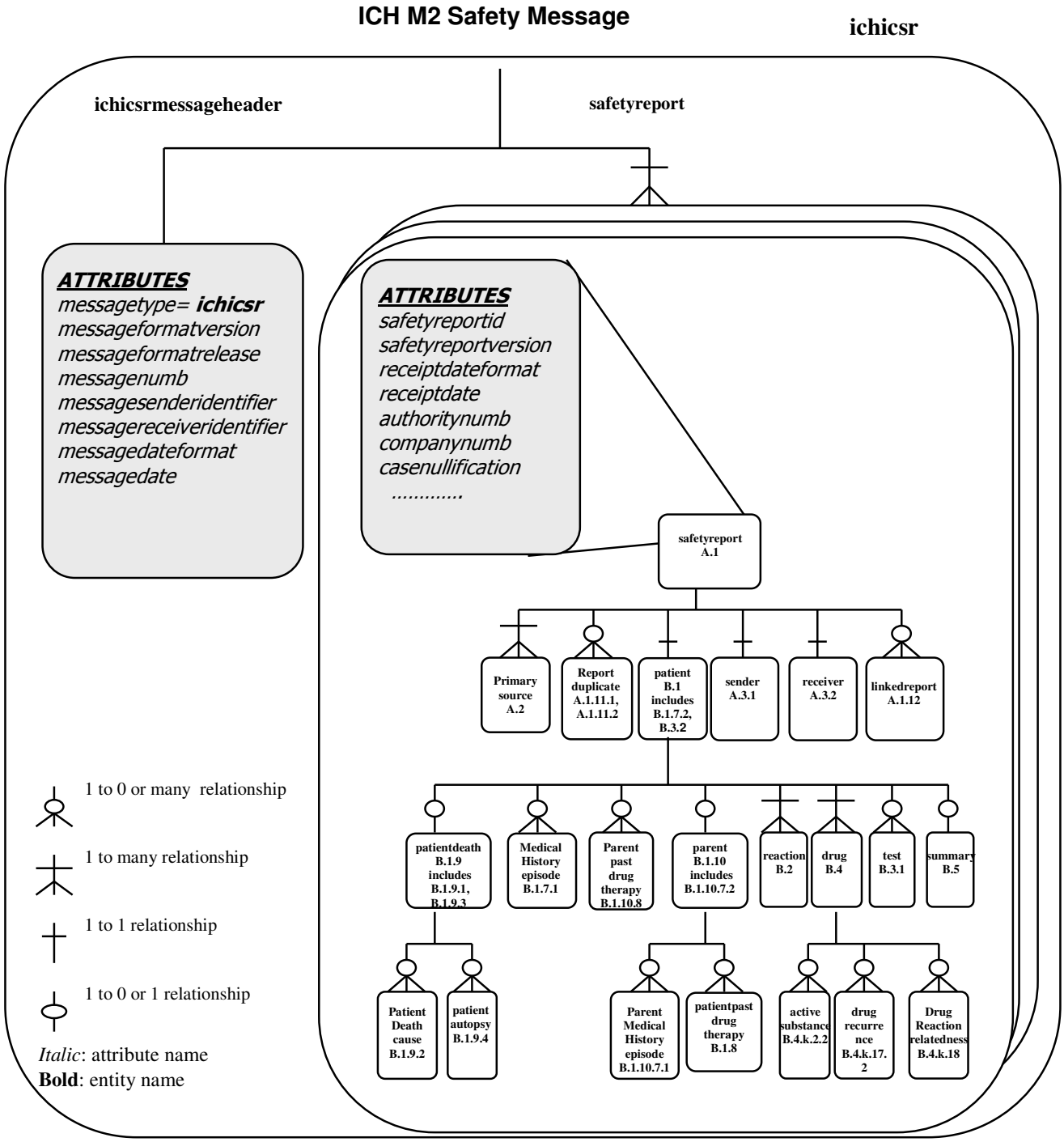


Figure 6

### 7.2 Individual Case Safety Report (ICSR)

The ICSR follows the ICH M2 Entities and Relationship diagram with the defined ICH M2 entities and their relationships to the ICH E2B(R2) data elements (Figure 7).

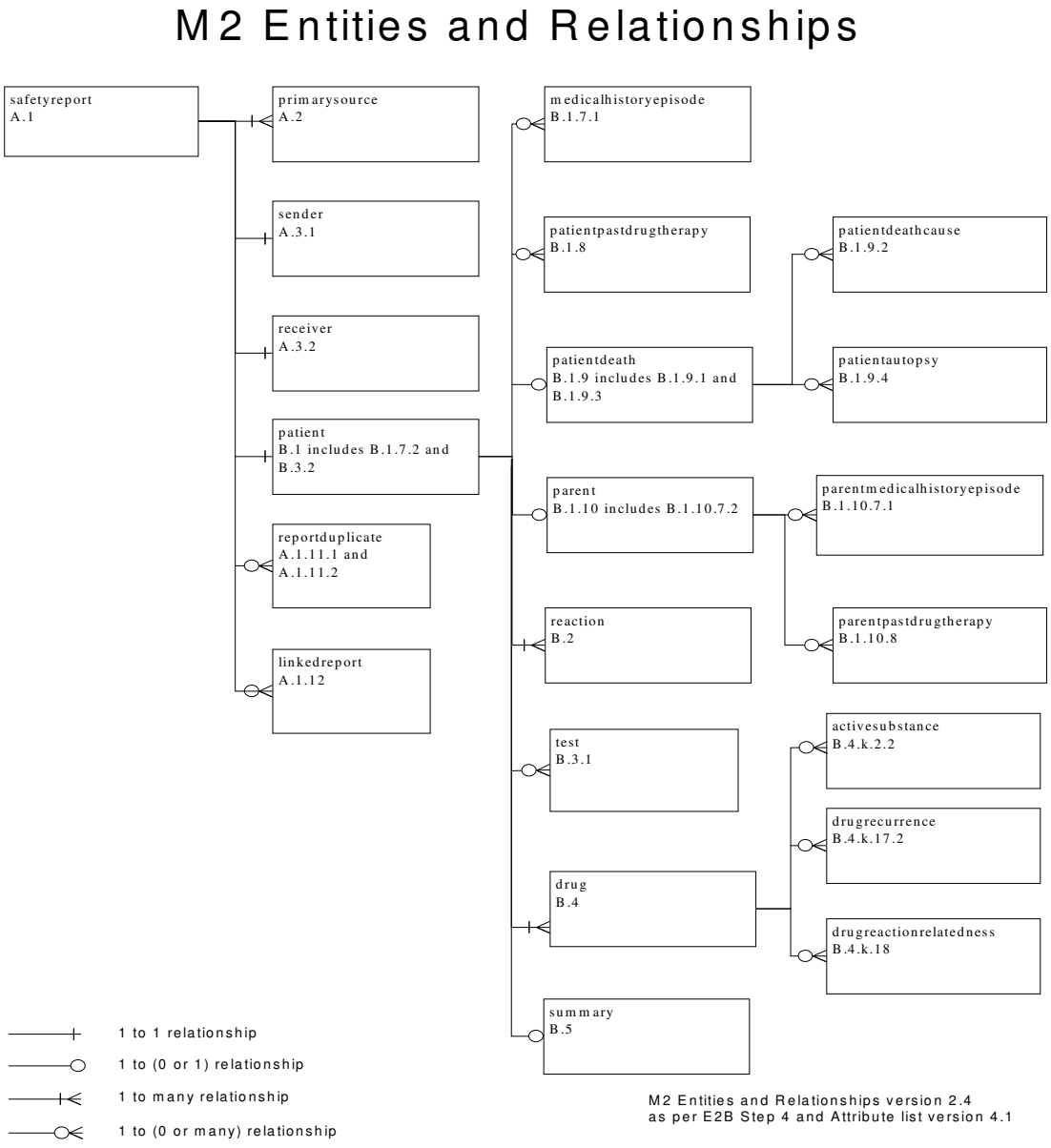


Figure 7

As shown in Figure 7, the schema for every ICSR in EV7.1 is organized following a hierarchical (parent-child) structure.

# 8 The Acknowledgment Message

This chapter describes the structure and the field values of an Acknowledgment Message created and returned to the sender by EV7.1. It provides the sender with the results of the outcome of the loading process and any detected errors and warnings.

The Acknowledgment structure respects the ICH ICSR specifications as described in the ICH M2 document 'Electronic Transmission of Individual Case Safety Report Message Specification version 2.3 (ICH ICSR DTD Version 2.1)'.

## 8.1 Acknowledgment Message Elements

An Acknowledgment Message contains the following elements presented in Table 1, as described in the ICH M2 document 'Electronic Transmission of Individual Case Safety Reports Message Specification Document Version 2.3', describing the fields of the acknowledgment message.

Table 1

| Data Element | DTD Descriptor | Field Length | Field Value | Mandatory |
|---|---|---|---|---|
| M.1 | Ichicsrmessageheader | | | |
| M.1.1 | Messagetype | 16AN | Ichicsrack | Yes |
| M.1.2 | Messageformatversion | 3AN | | Yes |
| M.1.3 | Messageformatrelease | 3AN | | 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<br>02 = ICSR Error, not all reports loaded into the database, check section B<br>03= SGML parsing error, no data extracted | Yes |
| A.1.7 | Parsingerrormessage | 250 AN | | |
| B.1. | Reportacknowledgment | | | |
| B.1.1 | Safetyreportid | 100AN | | |
| B.1.2 | safetyreportversion | 2AN | | |
| B.1.3 | Localreportnumber | 100AN | | |
| B.1.4 | Authoritynumber | 100AN | | |
| B.1.5 | companynumber | 100AN | | |
| B.1.7a | Receiptdateformat | 3N | 102 | |
| B.1.7b | Receiptdate | 8N | | |
| B.1.8 | Reportacknowledgmentcode | 2N | 01=Report Loaded Successfully<br>02=Report Not Loaded | Yes |
| B.1.9 | Errormessagecomment | 250AN | | |

**Comments:**

**Data Format Codes**

**102 = CCYYMMDD** *(example: 12 JANUARY 1997 --> 19970112)*
**204 = CCYYMMDDHHMMSS** *(example: 12 JANUARY 1997 14:02:17 --> 19970112140217)*

**Field Length**

Field Length is expressed in Char. 'N' means numeric values while 'AN' means alphanumeric values.

## 8.2 Acknowledgment Message elements descriptions

The elements descriptions (from ICH M2 'Electronic Transmission of Individual Case Safety Reports Message Specification (ICH ICSR DTD Version 2.1), Document Version 2.3' and ICH E2B(R2) 'Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSRS), Document Version 4.4.1') and the EV7.1 assigned values are the following:

### *8.2.1 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 SGML/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. It is specified in the Electronic Standards for the Transfer of Regulatory Information (ESTRI) recommendation 5.3. When creating an ICSR Acknowledgment SGML/XML message, the value of this field should be 'ichicsrack'.

- Default EV7.1 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 and is specified in the ESTRI recommendation 5.3. The value of the version number can be obtained from the ICSR Acknowledgment Message DTD.

- Default EV7.1 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 and is specified in the ESTRI recommendation 5.3. The value of the release number can be obtained from the documentation section of the ICSR Acknowledgment Message DTD.

- Default EV7.1 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.

- EV7.1 value is 'EU-EC-M-xxx-ACK' where xxx is the value 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 EV7.1 for an Acknowledgment Message is one of the following:
  - 'EVTEST' (Test environment – EVPM)
  - 'EVHUMAN' (Production environment – EVPM)
  - 'EVCTMTEST' (Test environment – EVCTM)
  - 'EVCTMPROD' (Production environment – EVCTM)

  depending to which module the original Safety Message was addressed.
- The value generated by EV7.1 for an Acknowledgment Message is identical to 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 EV7.1 for an Acknowledgment Message is identical to 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 EV7.1 value for the data element *messagedateformat* (ICH M2 M.1.7a) is '204' i.e., CCYYMMDDHHMMSS

### *8.2.2 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 SGML/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.

- EV7.1 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.

- EV7.1 internal unique number

### 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 acknowleged, ie., 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 EV7.1 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 EV7.1 is one of the following:
  - 'EVTEST' (Test environment – EVPM)
  - 'EVHUMAN' (Production environment – EVPM)
  - 'EVCTMTEST' (Test environment – EVCTM)
  - 'EVCTMPROD' (Production environment – EVCTM)

  depending to which module the original Safety Message was addressed.
- The value generated by EV7.1 is the same 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 *iscrmessagedate* (ICH M2 A.1.5b) is the date when the Safety Message was initiated.

- EV7.1 reports the same value as specified in the data element *messagedate* (ICH M2 M.1.7b) in the original incoming Safety Message.
- The default EV7.1 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.

- EV7.1 possible Transmission Acknowledgment Code values are:
  - 01 = All Reports loaded into database
  - 02 = ICSR Error, not all reports loaded into the database
  - 03 = SGML parsing error, no data extracted

### A.1.7 Parsing Error Message (See chapter 8.3 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 SGML/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'.

- EV7.1 reports potential parsing errors generated by the system's internal XML parser.

### *8.2.3 B.1. Report Acknowledgment*

This section header provides an acknowledgment for each ICSR included in the Safety Message file. This section specifies the elements to acknowledge the data format, data length, and data type, to ensure the information is loadable into the receiver's database (EV7.1). This section 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 EV7.1 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 is the number 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.

- The EV7.1 value in the Report Acknowledgment is the same as specified in the ICH E2B(R2) 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.

- EV7.1 reports for this data element 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.

- The EV7.1 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.

- EV7.1 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 (ICH E2B(R2): A.1.7)**

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

- EV7.1 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 EV7.1 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 2AN field.

- EV7.1 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 8.4 and 8.5 for more details)

The data element *errormessagecomment* (ICH M2 B.1.9) is a text field (250 characters) and it is populated by EV7.1 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 process of the ICSR, EV7.1 always adds the data element *errormessagecomment* (ICH M2 B.1.9) in the Report Acknowledgment section of every Acknowledgment Message.

## 8.3 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., no data extracted. This field describes the error generated by the EV7.1 XML parser.

### *8.3.1 Parsingerrormessage example*

The following section extracted from a Safety Message includes the element <xyz>, which is not included in the DTD specification. Below is an example for an Acknowledgment Message specifying the error detected by EV7.1 during the validation process.

**Message:**

```
<?xml version="1.0" encoding="iso-8859-1"?>
<!DOCTYPE ichicsr SYSTEM "http://ers.emea.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>DP2002042204</safetyreportid>
    ……..
```

**Acknowledgment:**

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

## 8.4 Errormessagecomment

The data element *errormessagecomment* (ICH M2 B.1.9) appears in the section *reportacknowledgment* (ICH M2 B.1), which is reported as often as the number of the ICSRs 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, EV7.1 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), EV7.1 describes the errors and warnings encountered during the validation process of the ICSR. Then EV7.1 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 process of the ICSR has detected warnings, their textual description is included in the data element *errormessagecomment* (ICH M2 B.1.9).

### *8.4.1 Errormessagecomment example (correct)*

If an ICSR is completely correct, without warnings, the following example shows the *errormessagecomment* as created by EV7.1:

**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>
.....
```

### *8.4.2 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>DP2002042204</safetyreportid>
<primarysourcecountry>FR</primarysourcecountry>
<occurcountry>FR</occurcountry>
<transmissiondateformat>999</transmissiondateformat>
<transmissiondate>20020422</transmissiondate>

.....

**Acknowledgment:**

.....

<reportacknowledgmentcode>02</reportacknowledgmentcode>
<errormessagecomment>safety report not loadedComments: 1- In section SAFETYREPORT on field transmissiondateformat value: 999 reported Error SCHEMA - Enumeration constraint failed. Enumeration constraint failed. The element: 'transmissiondateformat' has an invalid value according to its data type.; Parsing process: Report with Errors </errormessagecomment>

.....

### *8.4.3 Errormessagecomment example - warning*

The following example shows the possible Report Acknowledgment for an ICSR loaded with warnings (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; Comments: 1- In section DRUG on field medicinalproduct 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>

.....

## 8.5 Errormessagecomment Structure

Example of *Errormessagecomment* element structure for the Acknowledgement example described in chapter 8.4.3:

❶ Safety report loaded

❷ Comments:

❸ 1- In section DRUG on field medicinalproduct 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 Information:**

- Safety report loaded
- Safety report not loaded

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

Structure of the Errors/Warning Elements for the Acknowledgement example described in chapter 8.4.3:

*a. 1-*
*b. In section DRUG*
*c. on field medicinalproduct*
*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 9, ICSR Classification)**

❻ **Current Report Classification**

- Displays the EV7.1 report ID and the classification outcome

❼ **Old Report Classification**

- Displays the EV7.1 report ID which was previously stored in the system, and the reclassification status of the previously stored report.

### *8.5.1 Error description list*

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

#### *8.5.1.1 Unexpected element*

If the element 'xxx' is not expected in the document.

*Reason: Element found is not expected according to the DTD Schema.*

#### *8.5.1.2 Enumeration List Error*

If the element 'xxx' value is not part of a standard value list.

*Enumeration constraint failed. The element: 'xxx' has an invalid value according to its data type.*

#### *8.5.1.3 MaxInclusive Error*

If the element 'xxx' value is exceeding the maximum value allowed.

*MaxInclusive constraint failed. The element: 'xxx' has an invalid value according to its data type.*

#### *8.5.1.4 MaxLength*

If the element 'xxx' value's length is exceeding its maximum allowed.

*MaxLength constraint failed. The element: 'xxx' has an invalid value according to its data type.*

#### *8.5.1.5 MinInclusive Error*

If the element 'xxx' value is smaller than the minimum value allowed.

*MinInclusive constraint failed. The element: 'xxx' has an invalid value according to its data type.*

#### *8.5.1.6 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: 'xxx' ' has an invalid value according to its data type.*

#### *8.5.1.7 totalDigit Error*

If the element ‘xxx’ representing a decimal, exceeds the maximum number of admissible digits:
*totalDigits constraint failed. The element: ‘xxx’ has an invalid value according to its data type.*

#### *8.5.1.8 fractionDigit Error*

If the element ‘xxx’, representing a decimal, exceeds the maximum number of digits in the fractional part:
*fractionDigits constraint failed. The element: 'xxx' has an invalid value according to its data type.*

#### *8.5.1.9 DateLength Error*

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

#### *8.5.1.10 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).*

#### *8.5.1.11 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.*

#### *8.5.1.12 AtMostOne Error*

If at most one element can be present, but there is more than one element specified.
*At most one between authoritynumb or companynumb.*

#### *8.5.1.13 AtLeastOne Error*

If one element between n-elements must be present, but no element is specified.
*At least one between authoritynumb or companynumb.*

#### *8.5.1.14 LookupMedDRALLT Error*

If the element value (i.e. ‘xxx’), does not match with the MedDRA LLT lookup.
*‘xxx’ must be a valid MedDRA term.*

#### *8.5.1.15 LookupProducts Error*

If the element value (i.e. ‘xxx’), does not match with the Medicinal Product lookup.
*‘xxx’ must be a valid Medicinal Product.*

#### *8.5.1.16 LookupSubstance Error*

If the element value (i.e. ‘xxx’) does not match with the Active Substance lookup.
*‘xxx’ must be a valid activesubstance.*

#### *8.5.1.17 LookupDosageform Error*

If the element value (i.e. ‘xxx’) does not match with the Dosage Form lookup.
*‘xxx’ must be a valid dosageform.*

#### *8.5.1.18 LookupCountryCode Error*

If the element value (i.e. ‘xxx’) does not match the Country Code lookup.
*‘xxx’ must be a valid countrycode.*

#### *8.5.1.19 LookupLanguage Error*

If the element value (i.e. ‘xxx’) does not match the Language lookup.
*‘xxx’must be a valid language.*

#### *8.5.1.20 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.*

#### *8.5.1.21 PreviousDate*

If the element, that represents a date, indicates a future date.
*NOT Valid Date: future date (05/04/08).*

#### *8.5.1.22 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).*

#### *8.5.1.23 ElementNull Error*

If the element must be null as the value of another corresponding element requires this.
*The element must be null: It must be null, because e.g. the value of patientsex.*

#### *8.5.1.24 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.
*The element referred must contain a valid MedDRA version since a correlated MedDRA term has been used.*

# 9 ICSR Classification

The classification is a process in which EV7.1 manages the versioning of the incoming ICSRs. The classification rules are designed to maintain a concept in which 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 maintaining ICSRs, which have been nullified by the original sender, indicating the reasons for the nullification of a case.

## 9.1 Case Classification

A report may be classified as:

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

### *9.1.1 Case Report*

Case Report is a report describing a case for the first time (Initial report) or at a later time (Follow-up).

### *9.1.2 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.

### *9.1.3 Error Report*

Error Report is a report containing syntactic or semantic mistakes.

### *9.1.4 Nullified Report*

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

## 9.2 Classification algorithm

This chapter presents the classification algorithm based on the field values for nullifications, as well as the case number and the receipt date:

### *9.2.1 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*

*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*

### *9.2.2 Nullification Reports*

*If the nullification field of loading report =1*

*case number of loading report <> case number of pre-existing report*

⇨ *Type of loading report =error report*

*case number of loading report = case number of pre-existing report*

*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.

## Appendix A: Business Rules (Error Generation)

**Table Legend:**

- **DATA ELEMENT** Element (or session) standard code
- **NAME** Element (or session) standard name
- **MAX LENGTH** Max 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 1*
- **MANDATORY** Indicates that Element (or session) is mandatory (if nothing is specified, it is considered optional)
  - *If specified (1...∞) means that can be multiple*
- **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 3 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 E(2B) 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 the EVPM and EVCTM (Error Generation)

This table (Table 2) summarises the list of the business rules common to the EVPM and EVCTM, generating error messages by EV7.1 in case of non-compliance.

Table 2

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| M.1 | **ichicsrmessageheader** | | | | **Mandatory** | |
| M.1.1 | messagetype | 16 | AN | (ICHICSR, ICSR, ichicsr, icsr) | Mandatory | |
| M.1.2 | messageformatversion | 3 | AN | 2, 2.0, 2.1 | Mandatory | |
| M.1.3 | messageformatrelease | 3 | AN | 0, 0.0, 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 | |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| 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 | | Mandatory | |
| A.1.1 | primarysourcecountry | 2 | A | Lookup on ISO3166 | Mandatory | 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] | Mandatory | See note 2 |
| A.1.5.1 | Serious | 1 | N | (1,2) | Mandatory | Accepted value is (1) if one of A.1.5.2 values is (1) |
| A.1.5.2 | seriousnessdeath | 1 | N | (1,2) | Mandatory if A1.5.1 value is (1) and accepted value is (1) | |
| | seriousnesslifethreatening | 1 | N | (1,2) | | |
| | seriousnesshospitalization | 1 | N | (1,2) | | |
| | seriousnessdisabling | 1 | N | (1,2) | | |
| | Seriousnesscongenitalanomali | 1 | N | (1,2) | | |
| | seriousnessother | 1 | N | (1,2) | | |
| 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.1.10.1 | authoritynumb | 100 | AN | (valid ISO3166 country code-regulator name-report number) | | One of A.1.10.1 and A.1.10.2 See note 3 |
| A.1.10.2 | companynumb | 100 | AN | (valid ISO3166 country code-company name-report number) | | One of A.1.10.1 and A.1.10.2 See note 3 |
| A.1.14 | Medicallyconfirm | 1 | N | (1,2) | | See note 14 |
| 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.2.1.2f | reporterpostcode | 15 | 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.2.1.3 | 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] | Mandatory | See note 14 |
| 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 7 and 11 |
| A.2.3.2 | sponsorstudynumb | 35 | AN | | Mandatory for transmission to EVCTM | See note 11 |
| A.2.3.3 | observestudytype | 1 | N | (1,2,3) | Mandatory if A.1.4 value is (2). | See note 2 and 11 |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| A.3.1 | **sender** | | | | **Mandatory** | |
| A.3.1.2 | senderorganization | 60 | AN | | Mandatory | It is recommended to insert here the Sender's organisation ID. |
| 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.3.2.2a | 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.1.2.2b - 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.1.2.2b - 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.1.2.2b - 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.1.2.2b - 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 - B.1.2.2b - B.1.2.2.1a - B.1.2.3 - B.1.5 |
| 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.1.2.2b - 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.1.2.2.1a - B.1.2.2a and B.1.2.2b -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 | At least one of B.1.1-B.1.1.1a - B.1.1.1b - B.1.1.1c -B.1.1.1d - |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| | | | | | | B.1.2.1b -B.1.2.2a - B.1.2.2b - B.1.2.2.1a - B.1.2.3 - B.1.5 |
| 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.1.2.2b - 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 | |
| B.1.2.3 | patientagegroup | 1 | N | [1-6] | | 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.1.2.2b - 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) | | 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.1.2.2b -- B.1.2.2.1a - B.1.2.3 - B.1.5 |
| B.1.6a | lastmenstrualdateformat | 3 | N | (102,610,602) | | 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 |
| 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 | AN | Lookup on MedDRA LLTs | | See note 1 |
| B.1.7.1c | patientmedicalstartdate | 8 | N | Date | | Should precede B.1.7.1f and be conform to B.1.7.1b. See note 10 |
| 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.1.8c | patientdrugstartdate | 8 | N | Date | | Should precede B.1.8e and conform to B.1.8b. See note 10 |
| 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 | AN | Lookup on MedDRA LLTs | | See note 1 |
| B.1.8g.1 | patientdrgreactionmeddraversion | 8 | AN | x.x | Mandatory if B.1.8g.2 is not NULL. | See note 1 |
| B.1.8g.2 | patientdrugreaction | 250 | AN | Lookup on MedDRA LLTs | | See note 1 |
| 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 | See note1 |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| | | | | | NULL. | |
| B.1.9.2.b | patientdeathreport | 250 | AN | Lookup on MedDRA LLTs | | See note 1 |
| 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 | AN | Lookup on MedDRA LLTs | | See note1 |
| 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 | | | If not null, Should not be > 150 years. See note 5 |
| B.1.10.2.2b | parentageunit | 3 | N | (801) | Mandatory if B.1.10.2.2a is not NULL | |
| B.1.10.3a | Parentlastmenstrualdateformat | 3 | N | (102) | | 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) | | |
| B.1.10.7.1a.1 | parentmdepisodemeddraversion | 8 | AN | x.x | Mandatory if B.1.10.7.1a is not NULL. | See note 1 |
| B.1.10.7.1a.2 | parentmedicalepisodename | 250 | AN | Lookup on MedDRA LLTs | | See note 1 |
| B.1.10.7.1c | parentmedicalstartdate | 8 | N | Date | | Should precede B.1.10.7.1f and be conform to B.1.10.7.1b. See note 10 |
| 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.1.10.8c | parentdrugstartdate | 8 | N | Date | | Should precede B.1.10.8e and conform to B.1.10.8b. See note 10 |
| B.1.10.8e | parentdrugenddate | 8 | N | Date | | Should follow B.1.10.8c and conform to B.1.10.8d. See note 10 |
| B.1.10.8f.1 | parentdrgindicationmeddraversion | 8 | N | x.x | Mandatory if B.1.10.8f.2 is not NULL | See note 1 |
| B.1.10.8f.2 | parentdrugindication | 250 | AN | Lookup on MedDRA LLTs | | 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 | AN | Lookup on MedDRA LLTs | | See note1 |
| B.2 | **reaction** | | | | **Mandatory (1...∞)** | |
| B.2.i.1.a | reactionmeddraversionllt | 8 | AN | x.x | Mandatory | See note 1 |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| B.2.i.1.b | reactionmeddrallt | 250 | AN | Lookup on MedDRA LLTs | 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.4b | reactionstartdate | 12 | N | Date | | Should precede B.2.i.5b and conform to B.2.i.4a. See note 10 |
| 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 | |
| B.2.i.7.1b | reactionfirsttimeunit | 3 | N | [801-807] | Mandatory if B.2.i.7.1a is not NULL | |
| B.2.i.7.2b | reactionlasttimeunit | 3 | N | [801-807] | Mandatory if B.2.i.7.2a is not NULL | |
| B.2.i.8 | reactionoutcome | 1 | N | [1-6] | Mandatory | |
| B.3.1b | testdate | 8 | N | Date | | Should conform to B.3.1a. See note 10 |
| B.4 | **drug** | | | | **Mandatory (1...∞)** | |
| B.4.k.1 | drugcharacterization | 1 | N | (1,2,3) | 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. See note 12 |
| B.4.k.2.2 | activesubstancename | 100 | AN | Lookup on Substances (warning) | Mandatory if B.4.k.1 value is (1) or (3) | At least one of B.4.k.2.1 and B.4.k.2.2. 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 | |
| B.4.k.5.5 | drugintervaldosagedefinition | 3 | AN | (801,802,803,804, 805,806,807,810,811,812, 813) | | |
| B.4.k.5.7 | drugcumulativedosageunit | 3 | ~~AN~~ | | Mandatory if B.4.k.5.6 is not NULL | |
| B.4.k.10b | reactiongestationperiodunit | 3 | N | (802,803,804,810) | Mandatory if B.4.k.10a is not NULL | |
| 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 | AN | Lookup on MedDRA LLTs | | See note 1 |
| 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 | |
| B.4.k.13.2b | druglastperiodunit | 3 | N | [801-807] | Mandatory if B.4.k.13.2a is not NULL | |
| B.4.k.14b | drugenddate | 8 | N | Date | | Should follow B.4.k.12b and conform to B.4.k.14a. See note |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| | | | | | | 10 |
| B.4.k.15b | drugtreatmentdurationunit | 3 | N | [801-806] | Mandatory if B.4.k.15a is not NULL | |
| 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 | AN | Lookup on MedDRA LLTs | Mandatory if the section drugrecurrence is specified. See note 8 | See note 1 |
| B.4.k.18.1a | drugreactionassesmeddra version | 8 | AN | x.x | Mandatory if B.4.k.18.1b is not NULL. | See note 1 |
| B.4.k.18.1b | drugreactionasses | 250 | AN | Lookup on MedDRA LLTs | | It should be the same as one specified in B.2.i.1.b. See note 1 |
| B.5.3a | senderdiagnosismeddraversion | 8 | AN | x.x | Mandatory if B.5.3b is not NULL. | See note 1 |
| B.5.3b | senderdiagnosis | 250 | AN | Lookup on MedDRA LLTs | | See note 1 |

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

The following table (Table 3) summarises the list of the business rules specific to the EVPM only, generating error messages by EV7.1 in case of non-compliance.

Table 3

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| A.1.4 | Reporttype | 1 | N | (1,2,3,4) | Mandatory | See note 2 |
| A.1.5.2 | seriousnessdeath | 1 | N | (1,2) | Mandatory if A1.5.1 value is (1) and accepted value is (1) | Accepted value is (1) if one of B.2.i.8 value is (5). See note 6 |
| A.2.3.3 | Observestudytype | 1 | N | (2,3) | Mandatory if A.1.4 value is (2). | See note 2 |
| B.2.i.8 | reactionoutcome | 1 | N | [1-6] | 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 |

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

Table 4 summarises the list of the business rules specific to the EVCTM only, generating error messages by EV7.1 in case of non-compliance.

Table 4

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| A.1.4 | reporttype | 1 | N | (2) | Mandatory | See note 2 |
| A.2 | **primarysource** | | | | **Mandatory (1...∞)** | See note 11 |
| A.2.3.1 | studyname | 100 | AN | | Mandatory | See note 7 and 11 |
| A.2.3.2 | sponsorstudynumb | 35 | AN | | Mandatory | See note 11 |
| A.2.3.3 | observestudytype | 1 | N | (1) | Mandatory | See note 2 |

**NOTES:**

1. The supported MedDRA versions are related to the EV7.1 environment (EV7.1 test 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 EV7.1 test environment supports MedDRA version 4.0 and higher. The EV7.1 production environment supports the previous and the current MedDRA version. The validation process of the ICSRs accepts only current terms/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 alphanumeric MedDRA terms/codes generates an error message in the validation process.

2. 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 in order to obtain a successful outcome of the validation of the ICSRs (See paragraphs A.2 and A.3 above). Failure to the validation generates an error message.

   a) For ICSRs sent to the 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).

   b) For SUSARs sent to the 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).

3. 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 '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 to the validation of the first part of the concatenation ('valid ISO3166 country code-') generates an error message.

4. 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 *occurountry* (ICH E2B(R2) A.1.2).

5. 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. Any ICSR submitted to the EVPM 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)).

   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'.

   Failure to this validation in the EVPM will generate an error message.

   This validation is not applied to SUSARs submitted to the EVCTM.

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

   a) For SUSARs originating in the EEA:
   - 'Valid EudraCT Number#Study name' when the data elements *primarysourcecountry* (ICH E2B(R2) A.1.1) and/or *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 name' or 'Valid DMP EV Code#Study name' when the data elements *primarysourcecountry* (ICH E2B(R2) A.1.1) and/or *occurcountry* (ICH E2B(R2) A.1.2) are non-EEA countries.

   A valid EudraCT Number should match with an existing 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.

   A valid DMP EV code should match an existing EV Code attributed by the EudraVigilance Medicinal Product Dictionary (EVMPD) to a development medicinal product (DMP).

   A EudraCT Number will be provided on the EudraVigilance website for all clinical trials started before 01 May 2004 and including a center in an EEA country. It should be used in the data element *studyname* (ICH E2B(R2) A.2.3.1 for these clinical trials only.

   It is important to maintain the structure of the concatenation with the '#' symbol in the data element *studyname* (ICH E2B(R2) A.2.3.1) to obtain a successful outcome of the validation of this data element (See paragraph A.3 above). Failure to the validation with 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).

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

9. Data 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 to validation of the date format generates an error.
    - All dates except *messagedate* (ICH M2 M.1.7b) and *transmissiondate* (ICH E2B(R2) A.1.3b) cannot be greater than *receiptdate* (ICH E2B(R2) A.1.7b). Failure to 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), *drugstartdate* (ICH E2B(R2) B.1.8c) cannot be greater than the specified end date. Failure to 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) cannot be smaller than the start date. Failure to this validation generates an error.

11. *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 o*bservestudytype* (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 the EVCTM if these data elements are reported in at least one primary source section.

12. The presence of at least one of the data elements *medicinalproduct* (ICH E2B(R2) B4.k.2.1) or *activesubstancename* (ICH E2B(R2) B4.k.2.2) is mandatory. In each drug section, at least one of these data elements should appear, otherwise the validation performed by EV7.1 generates an error. The presence of the data element *activesubstancename* (ICH E2B(R2) B4.k.2.2) is mandatory when the value in the data element *drugcharacterisation* (ICH E2B(R2) B4.k.1) is '1' (suspect) or '3' (interacting). For combination products, the active ingredient section needs to be repeated as necessary.

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

14. 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:

    a) First primary source is a non-heath 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 heath 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.

Failure to this validation will generate an error message.

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 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 '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 drug and the reported 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.

## Appendix B: Business Rules (Warning Generation)

**Table Legend: See Appendix A**

This chapter reflects the list of the business rules (Table 5), generating warnings by EV7.1.

Table 5

| DATA ELEMENT | NAME | 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 | | See note 2 |
| B.1.10.8a | parentdrugname | 100 | AN | Lookup on Medicinal Products | | See note 2 |
| B.3.1c | testname | 100 | AN | Lookup on MedDRA LLTs | | See note 3 |
| B.3.1e | testunit | 35 | AN | | Mandatory if B.3.1d is not NULL | |
| B.4.k.2.1 | medicinalproduct | 70 | AN | Lookup on Medicinal Products | | At least one of B.4.k.2.1- B.4.k.2.2. See note 2 |
| B.4.k.2.2 | activesubstancename | 100 | AN | Lookup on Substances | Mandatory (error) if B.4.k.1 value is (1) or (3) | At least one of B.4.k.2.1- B.4.k.2.2. See note 2 |
| B.4.k.7 | drugdosageform | 100 | AN | Lookup on Dosage forms | | See note 4 |

**NOTES:**

1. If the length is over 5 characters the system generates a warning, otherwise if it is over 10 characters the system generates an error.
2. Warning refers only to the values associated to those elements. The presence of at least one of the data elements *medicinalproduct* (ICH E2B(R2) B4.k.2.1) or *activesubstancename* (ICH E2B(R2) B4.k.2.2) is mandatory. In each drug section, at least one of these data elements should appear, otherwise the validation performed by EV7.1 generates an error. The presence of the data element *activesubstancename* (ICH E2B(R2) B4.k.2.2) is mandatory when the value in the data element *drugcharacterisation* (ICH E2B(R2) B4.k.1) is '1' (suspect) or '3' (interacting). For combination products, the active ingredient section needs to be repeated as necessary.

   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.

3. The ICSRs including tests should report in the *testname* field (ICH E2B(R2) B.3.1c) a valid MedDRA term. The failure of a successful match with the MedDRA lookup for the *testname* field generates a warning.
4. 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 Pharmaceutical Forms list generates an warning. If the drug dosage form is not available in the latest version of the European Pharmacopoeia Pharmaceutical 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 validation process performed by EV7.1.

**Table Legend: See Appendix A**

### C.1 Rules applicable to the EVPM and EVCTM

Table 6 summarises the complete list of the business rules common to the EVPM and to EVCTM.

Table 6

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| M.1 | **ichicsrmessageheader** | | | | **Mandatory** | |
| M.1.1 | messagetype | 16 | AN | (ICHICSR, ICSR, ichicsr, icsr) | Mandatory | |
| M.1.2 | messageformatversion | 3 | AN | 2, 2.0, 2.1 | Mandatory | |
| M.1.3 | messageformatrelease | 3 | AN | 0, 0.0, 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 | |
| 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 | | Mandatory | |
| A.1.1 | primarysourcecountry | 2 | A | Lookup on ISO3166 | Mandatory | See note 16 |
| A.1.2 | occurcountry | 2 | A | Lookup on ISO3166 | | |
| 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] | Mandatory | See note 8 |
| A.1.5.1 | Serious | 1 | N | (1,2) | Mandatory | Accepted value is (1) if one of A.1.5.2 values is (1) |
| A.1.5.2 | seriousnessdeath | 1 | N | (1,2) | Mandatory if A1.5.1 value is (1) and accepted value is (1) | Accepted value is (1) if one of B.2.i.8 value is (5). See note 9 |
| | seriousnesslifethreatening | 1 | N | (1,2) | | |
| | seriousnesshospitalization | 1 | N | (1,2) | | |
| | seriousnessdisabling | 1 | N | (1,2) | | |
| | Seriousnesscongenitalanomali | 1 | N | (1,2) | | |
| | seriousnessother | 1 | N | (1,2) | | |
| 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) | | |
| A.1.8.2 | documentlist | 100 | AN | | | |
| A.1.9 | fulfillexpeditecriteria | 1 | N | (1,2) | | |
| A.1.10.1 | authoritynumb | 100 | AN | (valid ISO3166 country code-regulator name-report number) | | One of A.1.10.1 and A.1.10.2 See note 3 |
| A.1.10.2 | companynumb | 100 | AN | (valid ISO3166 country code-company name- | | One of A.1.10.1 and A.1.10.2 See note 3 |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| | | | | report number) | | |
| A.1.11 | duplicate | 1 | N | (1) | | |
| A.1.13 | casenullification | 1 | N | (1) | | |
| A.1.13.1 | nullificationreason | 200 | AN | | | |
| A.1.14 | Medicallyconfirm | 1 | N | (1,2) | | See note 10 |
| | **reportduplicate** | | | | | |
| A.1.11.1 | duplicatesource | 50 | AN | | | |
| A.1.11.2 | duplicatenumb | 100 | AN | | | |
| | **linkedreport** | | | | | |
| A.1.12 | linkreportnumb | 100 | AN | | | |
| 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.2.1.4, 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.2.1.4, 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 | | | |
| A.2.1.2f | reporterpostcode | 15 | AN | | | At least one of A.2.1.1d, A.2.1.2a, A.2.1.2f, A.2.1.3, A.2.1.4, A.2.2, A.2.3.1 |
| 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.2.1.4, A.2.2, A.2.3.1 |
| A.2.1.4 | qualification | 1 | N | [1-5] | 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.2.1.4, A.2.2, A.2.3.1 |
| A.2.3.1 | studyname | 100 | AN | | | Mandatory for any transmission to EVCTM. See note 13 and 17 |
| A.2.3.2 | sponsorstudynumb | 35 | AN | | | See note 17 |
| A.2.3.3 | observestudytype | 1 | N | (1,2,3) | | 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] | | |
| A.3.1.2 | senderorganization | 60 | AN | | Mandatory | It is recommended to insert here the Sender's organisation id as requested in EudraVigilance, even if there is no business check on this field. |
| 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 | | | |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| A.3.1.4g | sendertelextension | 10 | AN | | | See note 5 |
| A.3.1.4h | sendertelcountrycode | 3 | AN | | | |
| A.3.1.4i | senderfax | 10 | AN | | | |
| A.3.1.4j | senderfaxextension | 10 | AN | | | See note 5 |
| 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) | | |
| 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 |
| A.3.2.3h | receivertelcountrycode | 3 | AN | | | |
| A.3.2.3i | receiverfax | 10 | AN | | | |
| A.3.2.3j | receiverfaxextension | 10 | AN | | | See note 5 |
| 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.1.2.2b - 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.1.2.2b - 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.1.2.2b - 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.1.2.2b - 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 - B.1.2.2b - B.1.2.2.1a - B.1.2.3 - B.1.5 |
| B.1.2.1a | patientbirthdateformat | 3 | N | (102) | | 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.1.2.2b - 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 - |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| | | | | | | B.1.1.1c -B.1.1.1d - B.1.2.1b - B.1.2.2.1a - B.1.2.2a and B.1.2.2b -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] | | 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.1.2.2b - B.1.2.2.1a - B.1.2.3 - B.1.5 Mandatory if B.1.2.2a is not NULL |
| B.1.2.2.1a | gestationperiod | 3 | N | | | |
| B.1.2.2.1b | gestationperiodunit | 3 | N | (802,803,804,810) | | Mandatory if B.1.2.2.1a is not NULL |
| B.1.2.3 | patientagegroup | 1 | N | [1-6] | | 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.1.2.2b - 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) | | 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.1.2.2b -- B.1.2.2.1a - B.1.2.3 - B.1.5 |
| B.1.6a | lastmenstrualdateformat | 3 | N | (102,610,602) | | Should be NULL if B.1.5 value is (1) (patient is male). 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.1.7.2 | patientmedicalhistorytext | 10000 | AN | | | |
| B.1.7 | **medicalhistoryepisode** | | | | | |
| 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 | AN | Lookup on MedDRA LLTs | | See note 4 |
| B.1.7.1b | patientmedicalstartdateformat | 3 | N | (102,610,602) | | See note 1 |
| B.1.7.1c | patientmedicalstartdate | 8 | N | Date | | Should precede B.1.7.1f and be conform to B.1.7.1b. See note 15 |
| B.1.7.1d | patientmedicalcontinue | 1 | N | (1,2,3) | | |
| B.1.7.1e | patientmedicalenddateformat | 3 | N | (102,610,602) | | 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.1.8 | **patientpastdrugtherapy** | | | | | |
| B.1.8a | patientdrugname | 100 | AN | Lookup on Medicinal Products | | See note 2 |
| B.1.8b | patientdrugstartdateformat | 3 | N | (102,610,602) | | See note 1 |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| 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) | | 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 | AN | Lookup on MedDRA LLTs | | See note 4 |
| B.1.8g.1 | patientdrgreactionmeddraversion | 8 | AN | x.x | | Mandatory if B.1.8g.2 is not NULL. See note 4 |
| B.1.8g.2 | patientdrugreaction | 250 | AN | Lookup on MedDRA LLTs | | See note 4 |
| B.1.9 | **patientdeath** | | | | | |
| B.1.9.1a | patientdeathdateformat | 3 | N | (102,610,602) | | See note 1 |
| B.1.9.1b | patientdeathdate | 8 | N | Date | | Should conform to B.1.9.1a. See note 15 |
| B.1.9.3 | patientautopsyyesno | 1 | N | (1,2,3) | | |
| | **patientdeathcause** | | | | | |
| B.1.9.2.a | 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 | AN | Lookup on MedDRA LLTs | | See note 4 |
| | **patientautopsy** | | | | | |
| 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 | AN | Lookup on MedDRA LLTs | | See note 4 |
| B.1.10 | **parent** | | | | | |
| B.1.10.1 | parentidentification | 10 | AN | | | |
| B.1.10.2.1a | parentbirthdateformat | 3 | N | (102) | | 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 | | | If not null, Should not be > 150 years. See note 11 |
| B.1.10.2.2b | parentageunit | 3 | N | (801) | | Mandatory if B.1.10.2.2a is not NULL |
| B.1.10.3a | Parentlastmenstrualdateformat | 3 | N | (102) | | 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) | | |
| B.1.10.7.2 | parentmedicalrelevanttext | 10000 | AN | | | |
| B.1.10.7 | **parentmedicalhistoryepisode** | | | | | |
| B.1.10.7.1a.1 | parentmdepisodemeddraversion | 8 | AN | x.x | | Mandatory if B.1.10.7.1a is not NULL. See note 4 |
| B.1.10.7.1a. | parentmedicalepisodenam | 250 | AN | Lookup on | | See note 4 |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| 2 | e | | | MedDRA LLTs | | |
| B.1.10.7.1b | parentmedicalstartdateformat | 3 | N | (102,610,602) | | See note 1 |
| B.1.10.7.1c | parentmedicalstartdate | 8 | N | Date | | Should precede B.1.10.7.1f and be conform to B.1.10.7.1b. See note 15 |
| B.1.10.7.1d | parentmedicalcontinue | 1 | N | (1,2,3) | | |
| B.1.10.7.1e | parentmedicalenddateformat | 3 | N | (102,610,602) | | 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.1.10.8 | **parentpastdrugtherapy** | | | | | |
| B.1.10.8a | parentdrugname | 100 | AN | Lookup on Medicinal Products | | See note 2 |
| B.1.10.8b | parentdrugstartdateformat | 3 | N | (102,610,602) | | 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) | | 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 | parentdrgindicationmeddraversion | 8 | N | x.x | | Mandatory if B.1.10.8f.2 is not NULL. See note 4 |
| B.1.10.8f.2 | parentdrugindication | 250 | AN | Lookup on MedDRA LLTs | | See note 4 |
| B.1.10.8g.1 | parentdrgreactionmeddraversion | 8 | AN | x.x | | Mandatory if B.1.10.8g.2 is not NULL. See note 4 |
| B.1.10.8g.2 | parentdrugreaction | 250 | AN | Lookup on MedDRA LLTs | | 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 | AN | Lookup on MedDRA LLTs | 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) | | |
| B.2.i.4a | reactionstartdateformat | 3 | N | (102,203,610,602) | | 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) | | 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 |
| 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 |
| 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 |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| | | | | | | is not NULL |
| B.2.i.8 | reactionoutcome | 1 | N | [1-6] | 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) | | See note 1 |
| B.3.1b | testdate | 8 | N | Date | | Should conform to B.3.1a. See note 15 |
| B.3.1c | testname | 100 | AN | Lookup on MedDRA LLTs | | See note 14 |
| B.3.1d | testresult | 50 | AN | | | |
| B.3.1e | testunit | 35 | AN | | | Mandatory 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) | | |
| B.3.2 | resultstestsprocedures | 2000 | AN | | | |
| B.4 | **drug** | | | | **Mandatory (1...∞)** | |
| B.4.k.1 | drugcharacterization | 1 | N | (1,2,3) | 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 | | At least one of B.4.k.2.1- B.4.k.2.2 See note 2 |
| B.4.k.2.2 | activesubstancename | 100 | AN | Lookup on Substances | Mandatory if B.4.k.1 value is (1) or (3) | At least one of B.4.k.2.1 and B.4.k.2.2 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 |
| 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) | | |
| B.4.k.5.6 | drugcumulativedosagenumb | 10 | N | | | |
| B.4.k.5.7 | drugcumulativedosageunit | 3 | ~~A~~N | | | Mandatory if B.4.k.5.6 is not NULL |
| B.4.k.6 | drugdosagetext | 100 | AN | | | |
| B.4.k.7 | drugdosageform | 100 | AN | Lookup on Dosage forms | | See note 12 |
| B.4.k.8 | drugadministrationroute | 3 | N | [001-067] | | |
| B.4.k.9 | drugparadministration | 3 | N | [001-067] | | |
| 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 |
| 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 | AN | Lookup on MedDRA LLTs | | See note 4 |
| B.4.k.12a | drugstartdateformat | 3 | N | (102,610,602) | | See note 1 |
| 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 | | | |

| DATA ELEMENT | NAME | MAX LENGTH | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| B.4.k.13.1b | drugstartperiodunit | 3 | N | [801-807] | | Mandatory if B.4.k.13.1a is not NULL |
| 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 |
| B.4.k.14a | drugenddateformat | 3 | N | (102,610,602) | | 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 |
| B.4.k.16 | actiondrug | 1 | N | (1,2,3,4,5,6) | | |
| B.4.k.17.1 | drugrecurreadministration | 1 | N | (1,2,3) | | |
| B.4.k.19 | drugadditional | 100 | AN | | | |
| | **drugrecurrence** | | | | (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 | AN | Lookup on MedDRA LLTs | Mandatory if the section drugrecurrence is specified. (See note 6 | See note 4 |
| B.4.k.18 | **drugreactionrelatedness** | | | | | |
| B.4.k.18.1a | drugreactionassesmeddra version | 8 | AN | x.x | | Mandatory if B.4.k.18.1b is not NULL. See note 4 |
| B.4.k.18.1b | drugreactionasses | 250 | AN | Lookup on MedDRA LLTs | | It should be the same as one specified in B.2.i.1.b. See note 4 |
| B.4.k.18.2 | drugassessmentsource | 60 | AN | | | |
| B.4.k.18.3 | drugassessmentmethod | 35 | AN | | | |
| B.4.k.18.4 | drugresult | 35 | 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 | AN | Lookup on MedDRA LLTs | | See note 4 |
| B.5.4 | sendercomment | 2000 | AN | | | |

## C.2 Rules applicable to the EVPM only

The following table (Table 7) presents the complete list of the business rules specific to the EVPM only.

Table 7

| DATA ELEMENT | NAME | MAX LEN | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| A.1.4 | Reporttype | 1 | N | (1,2,3,4) | Mandatory | See note 8 |
| A.1.5.2 | seriousnessdeath | 1 | N | (1,2) | Mandatory if A1.5.1 value is (1) and accepted value is (1) | Accepted value is (1) if one of B.2.i.8 value is (5). See note 9 |
| A.2.3.3 | Observestudytype | 1 | N | (2,3) | | Mandatory if A.1.4 value is (2). See note 8 and 17 |
| B.2.i.8 | reactionoutcome | 1 | N | [1-6] | 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 |

## C.3 Rules applicable to the EVCTM only

The following table (Table 8) summarises the complete list of the business rules specific to the EVCTM only.

Table 8

| DATA ELEMENT | NAME | MAX LEN | TYPE | VALUES | MANDATORY | NOTES |
|---|---|---|---|---|---|---|
| A.1.4 | reporttype | 1 | N | (2) | Mandatory | See note 8 |
| A.2 | **primarysource** | | | | **Mandatory (1...∞)** | |
| A.2.3.1 | studyname | 100 | | AN | Mandatory | See note 13 and 17 |
| A.2.3.2 | sponsorstudynumb | 35 | AN | | Mandatory | See note 17 |
| A.2.3.3 | observestudytype | 1 | N | (1) | Mandatory | See note 8 and 17 |

**NOTES:**

1. **Data 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***

Warning refers only to the values associated to those elements. Their presence in at least one of the data elements *medicinalproduct* (ICH E2B(R2) B4.k.2.1) or *activesubstancename* (ICH E2B(R2) B4.k.2.2), is mandatory. In each drug section, at least one of these data elements should appear, otherwise the validation performed by EV7.1 generates an error. The presence of the data element *activesubstancename* (ICH E2B(R2) B4.k.2.2) is mandatory when the value in the data element

*drugcharacterisation* (ICH E2B(R2) B4.k.1) is '1' (suspect) or '3' (interacting). For combination products, the active ingredient section needs to be repeated as necessary.

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.

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 '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 to the validation of the first part of the concatenation ('valid ISO3166 country code-') generates an error message.

4. **MedDRA Versions**

   The supported MedDRA versions are related to the EV7.1 environment (EV7.1 test 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 EV7.1 test environment supports MedDRA version 4.0 and higher. The EV7.1 production environment supports the previous and the current MedDRA version. The validation process of the ICSRs accepts only current terms/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 alphanumeric MedDRA terms/codes generates an error message in the validation process.

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

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

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

   The section *drugrecurrence* 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 reported in the data element *reactionmeddrapt* (ICH E2B(R2) B.2.i.2.b). The EudraVigilance system does not store this information. The EudraVigilance 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 in order to obtain a successful outcome of the validation of the ICSRs (See paragraph A.2 and A.3 in Appendix A). Failure to the validation generates an error message.

a) For ICSRs sent to the 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),

b) For SUSARs sent to the 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).

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

Any ICSR submitted to the EVPM 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)).

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'.

Failure to this validation in the EVPM will generate an error message.

This validation is not applied to SUSARs submitted to the EVCTM.

10. ***medicallyconfirm***

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:

a) First primary source is a non-heath 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 heath 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.

Failure to this validation will generate an error message.

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 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 '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 drug and the reported 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.

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 Pharmaceutical Forms list generates an warning. If the drug dosage form is not available in the latest version of the European Pharmacopoeia Pharmaceutical Forms list or is under proposal, the information should only be entered in the data element *narrativeincludeclinical* (ICH M2 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 in the EEA:

- 'Valid EudraCT Number#Study name' when the data elements *primarysourcecountry* (ICH E2B(R2) A.1.1) and/or *occurcountry* (ICH E2B(R2) A.1.2) are EEA countries. Failure to enter a valid EudraCT Number will generate an error message,

b) For SUSARs originating outside the EEA:

- 'Valid EudraCT Number#Study name' or 'Valid DMP EV Code#Study name' when the data elements *primarysourcecountry* (ICH E2B(R2) A.1.1) and/or *occurcountry* (ICH E2B(R2) A.1.2) are non-EEA countries.

A valid EudraCT Number should match with an existing 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.

A valid DMP EV code should match an existing EV Code attributed by the EudraVigilance Medicinal Product Dictionary (EVMPD) to a development medicinal product (DMP).

A EudraCT Number will be provided on the EudraVigilance website for all clinical trials started before 01 May 2004 and including a center in an EEA country. It should be used in the data element *studyname* (ICH E2B(R2) A.2.3.1 for these clinical trials only.

It is important to maintain the structure of the concatenation with the '#' symbol in the data element *studyname* (ICH E2B(R2) A.2.3.1) to obtain a successful outcome of the validation of this data element (See paragraph A.3 above). Failure to the validation 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).

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 term. The failure of a successful match with the MedDRA lookup for the *testname* field generates a warning.

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 to validation of the date format generates an error.
- All dates except *messagedate* (ICH M2 M.1.7b) and *transmissiondate* (ICH E2B(R2) A.1.3b) cannot be greater than *receiptdate* (ICH E2B(R2) A.1.7b). Failure to 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), *drugstartdate* (ICH E2B(R2) B.1.8c)

cannot be greater than the specified end date. Failure to 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) cannot be smaller than the start date. Failure to this validation generates an error.

16. **Primary source country**

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 o*bservestudytype* (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 the EVCTM if these data elements are reported in at least one primary source section.

## 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 the 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 process, the medicinal product(s) and active substance(s) reported in the ICSRs are validated against the 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 will nevertheless be loaded in the EudraVigilance database and flagged as "Not Fully Recoded". The ICSRs validation steps performed by the EudraVigilance system are presented in Figure 8.

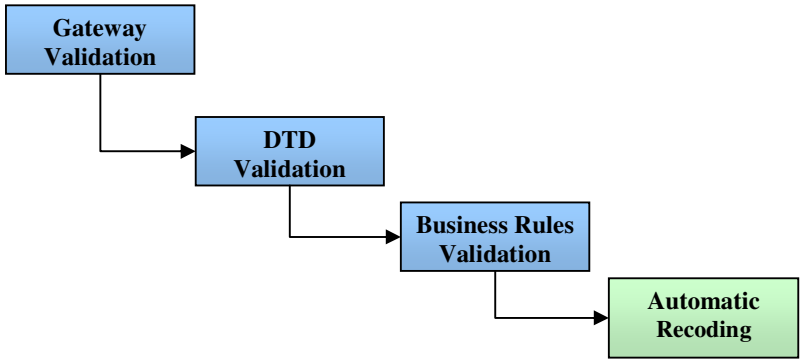


Figure 8

The ICH E2B(R2) fields on which the Automatic Recoding is performed are listed in the table below.

Table 9

| Name | ICH E2B(R2) Data element | Automatic Recoding (Reference Source) |
|---|---|---|
| *patientpastdrugtherapy: patientdrugname* | B.1.8a | EVMPD |
| *parentpastdrugtherapy: 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 the 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 has been developed by the EMEA in collaboration with its stakeholders and has been deployed in production in December 2001. In May 2004, the EVMPD has been 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 the implementing texts, in particular the "Detailed Guidance on the European Clinical Trials Database (EUDRACT Database)".

The objective of the EVMPD is to assist the safety monitoring activities in the EEA by coding medicinal products and active substances in ICSRs, which are reported to the EudraVigilance Clinical Trial Module (EVCTM) or to the EudraVigilance Post-Authorisation Module (EVPM).

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).

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 a 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 a clinical trial, which does not have a marketing authorisation in the EEA, and to which special confidentiality arrangements 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 a 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 development medicinal products subject to investigation in clinical trials. The three different databases are presented in Figure 9

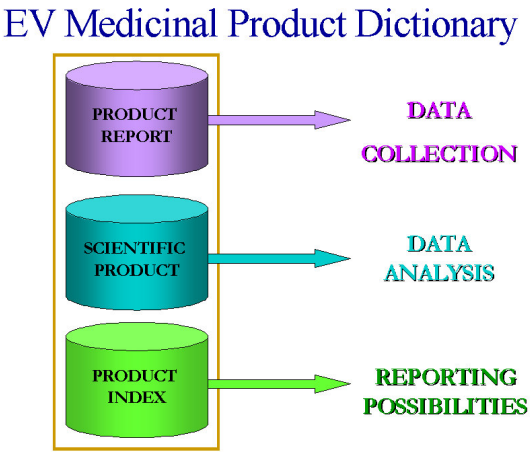


Figure 9

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 clinical trials. The Product Report Database generates the Product Index Database and the Scientific Product Database. Both support the validation and analysis of medicinal products and active substances reported in ICSRs.

The ***Scientific Product Database*** provides a hierarchy for the classification of all medicinal products (either with development or authorised status) registered in the EVMPD on the basis of the active substance(s), the strength of the active substance(s) and the pharmaceutical dose 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.

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 dose form(s);

- ***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 dose form(s).

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 the 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.

'Reporting possibilities' generated from development medicinal products and from development substances are treated as confidential which means that such 'reporting possibilities' can only be used for reporting of ICSRs by the owner of the development medicinal product or the development substance. The owner refers to the sponsor organisation, which entered the information in the EVMPD.

## 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 generated 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 elements based on the *Full Presentation Name* are:

- Product short name
- Product generic name (if applicable)
- Product strength (if applicable)
- Product pharmaceutical form (if applicable)
- Product MAH (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 often reported in the data element '*medicinalproduct'* (ICH E2B(R2) B.4.k.2.1), the Product Index Database also contains the Substances Names of the approved substances entered in the EVMPD [See D.5.1-Approved Substances].

**<u>Authorised Medicinal Product Example</u>**

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

| | |
|---|---|
| Product Full Presentation Name: | XYZ Tablets 500 mg |
| Product Short Name (*): | XYZ |
| Product Strength (*): | XYZ 500 mg |
| Product Pharmaceutical Form (*) | XYZ Tablets |

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

The Scientific Product Database and the Product Report 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 (reference is the SmPC).

Based on the SmPC of 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 500 mg Tablet

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:

- XYZ
- XYZ Tablets
- XYZ 500 mg
- XYZ Tablets 500mg
- Acetylsalicylic Acid
- Acetylsalicylic Acid 500 mg
- Acetylsalicylic Acid Tablets
- Acetylsalicylic Acid 500mg Tablets

The Product Index entries represent different 'reporting possibilities' to be entered in ICSRs and are used during the Automatic Recoding.

### D.4.2 Development Medicinal Products

For Development Medicinal Products the 'reporting possibilities' are created based on elements related to development medicinal products:

- 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 often 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 the EVMPD [See D.5.2-Development Substances].

**Development Medicinal Product Example**

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

**Product Code (*):** CTX5132/25
**Product Name:** (not available)
**Product Other Name**: (not specified as not available)
(*) as part of the product description as referred to in the Clinical Trial Application

The Scientific Product Database and the Product Report 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
- CTX5132
- CTX5132 25 mg
- CTX5132 capsule
- CTX5132 25 mg capsule

These 'reporting possibilities' are confidential, which means that they are only available for reporting by the sponsor organisation, which entered the development medicinal product in the 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 the Table 10

**Example for Approved Substances:**

Table 10

| **Approved Substance** | | |
|---|---|---|
| **Substance EV Code** | SUB09611MIG | |
| **Substance Type** | Approved | |
| **Substance Name** | Paracetamol<br>[*Reference Source: INN*] | |
| **Substance Translations** | | |
| **Translation** | Paracetamolum | [*Latin*] |
| **Translation** | Paracétamol | [*French*] |
| **Translation** | Paracetamol | [*Spanish*] |
| **Translation** | Paracetamol | [*Portuguese*] |
| **Translation** | Paracetamolo | [*Italian*] |
| **Substance Aliases** | | |
| **Alias** | Acetaminophen<br>[*Reference Source:Martindale*] | |
| **Alias Translation** | Acetaminofene [*Italian*] | |

### D.5.2 Development Substances

For Development Substances the 'reporting possibilities' are generated from the Product 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 the EVMPD.
See example in the Table 11

**Example for Development Substances**

Table 11

| **Development Substance** | | |
|---|---|---|
| **Substance EV Code** | SUB99999 | |
| **Substance Type** | Development | |
| **OwnerID (= SenderID)** | SPONS_ABC | |
| **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** | SUB_XYZ_II | [*as Name*] |
| **Previous Name/Code** | XYZ | [*as Code*] |

## 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 the 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 EVCODE 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].

If the validation against the Product Index Database at medicinal product level fails a validation at active substance level is also performed. If the reported medicinal product information matches one of the 'Reporting Possibilities' for active substances, the association with the relevant entry in the Product Index Database is created [See D.5- Product Index Database and 'Reporting Possibilities' for Active Substances].

### 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 EVCODE of the corresponding Product Index entry associated to the medicinal product reported in the 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 schema provided in Figure 10.

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

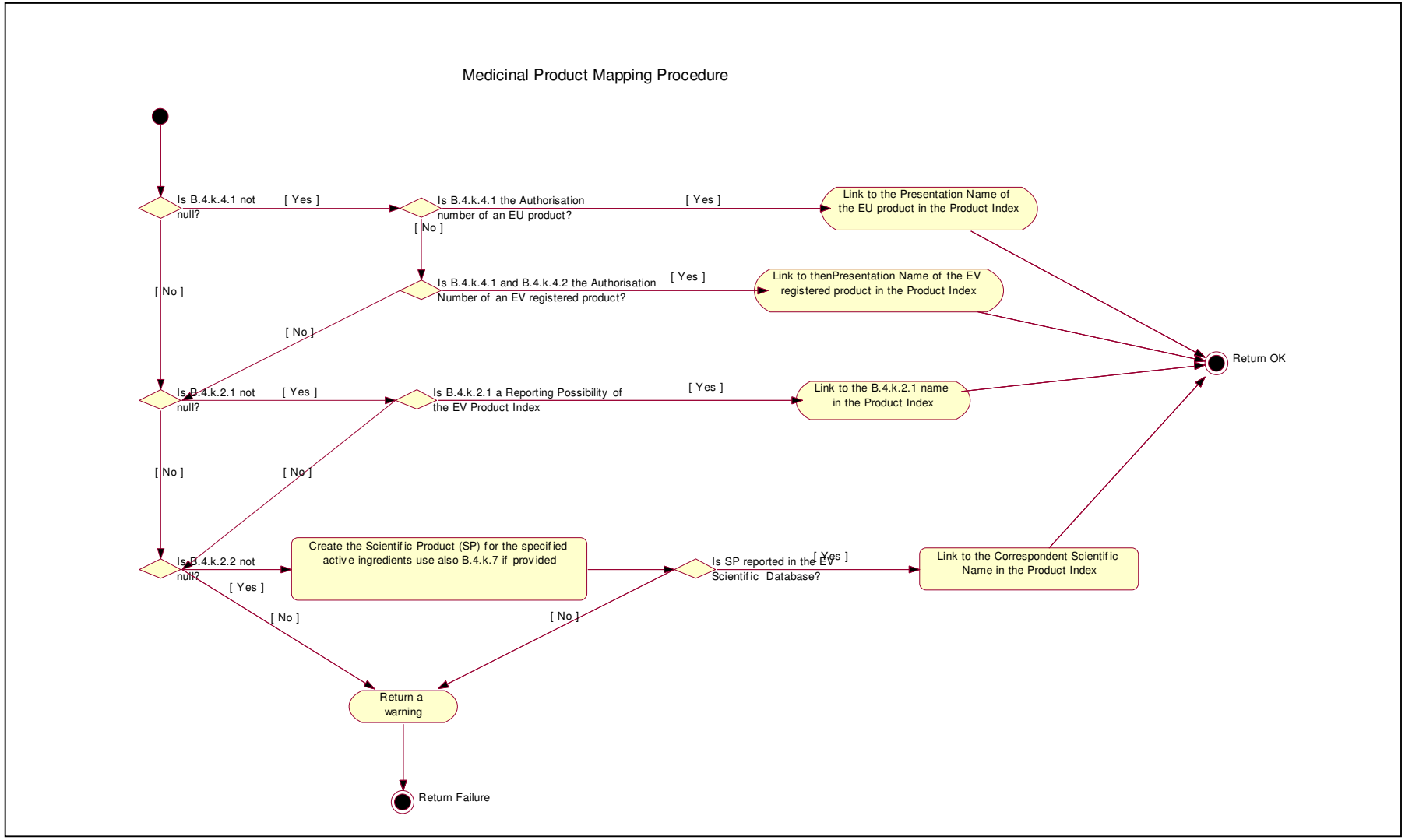
Medicinal Product Mapping Procedure
Is B.4.k.4.1 not null?
[ Yes ]
Is B.4.k.4.1 the Authorisation number of an EU product?
[ Yes ]
Link to the Presentation Name of the EU product in the Product Index
[ No ]
[ No ]
Is B.4.k.4.1 and B.4.k.4.2 the Authorisation Number of an EV registered product?
[ Yes ]
Link to thenPresentation Name of the EV registered product in the Product Index
[ No ]
Return OK
Is B.4.k.2.1 not null?
[ Yes ]
Is B.4.k.2.1 a Reporting Possibility of the EV Product Index
[ Yes ]
Link to the B.4.k.2.1 name in the Product Index
[ No ]
[ No ]
Is B.4.k.2.2 not null?
Create the Scientific Product (SP) for the specified active ingredients use also B.4.k.7 if provided
Is SP reported in the EV Scientific Database?
[ Yes ]
Link to the Correspondent Scientific Name in the Product Index
[ Yes ]
[ No ]
[ No ]
Return a warning
Return Failure

Figure 10

## 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 the EVMPD. This is achieved by retrieving the corresponding active substance EVCODE from the EVMPD.

The Automatic Recoding checks the reported active substance against the 'Reporting Possibilities' of the Product Indext Database which includes all approved and development substances entered in the 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 the EMEA.

## 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 the 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 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 the EVCTM.

## D.9 Reporting of Blinded Products

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'[4]. The drug section is further flagged as 'BLINDED PRODUCT'.

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

[4] The search for the prefix 'BLINDED' is case insensitive

## Appendix E: EudraVigilance Data Security

Once Safety Messages are sent to EV7.1 and loaded into the database they become available for query purposes to EV7.1 users.

EV7.1 users need to be individually registered with EV7.1 in order to be able to access the data, taking into account different levels of access rights to the data stored in EV7.1.

When EV7.1 receives a query from a user, security checks are performed, as not all ICSRs are visible to all users. EV7.1 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 can only see the ICSRs, that this particular MAH has submitted to EV7.1;
2. A user belonging to a NCA can see all ICSRs stored in EV7.1, independent of the fact that the ICSRs were submitted by a MAH, applicant or sponsor or another NCA.

The following example reflects the typical behaviour of the sender-based security. EV7.1 flags ICSRs with the ownership as displayed in Figure 11. In this example 'A' represents a MAH, 'B' represents a NCA.

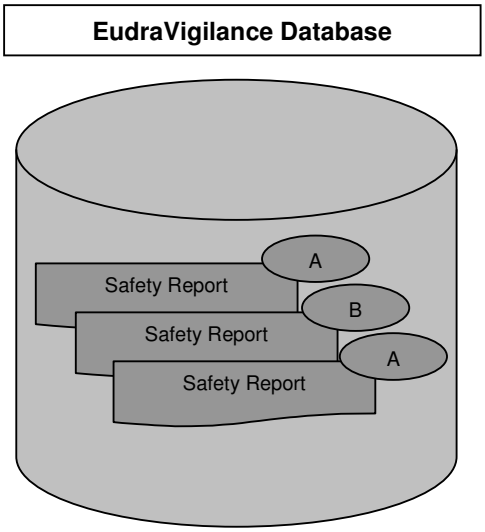


Figure 11

When a user belonging to the MAH 'A', is accessing EV7.1 and is performing a query on the ICSRs stored in EV7.1, the security filter will operate on the ICSRs that were returned as a result of the query as presented in the following table:

Table 12

| Safety Report ID | Owner |
|---|---|
| EU-EC-001 | A |
| EU-EC-003 | A |

EV7.1 returns only those ICSRs flagged with the ownership of organisation A, i.e. ICSRs sent by the MAH 'A'.

The data retrieved by the same query, considering that it is performed by a user belonging to a NCA 'B', would appear as presented in the next table:
Table 13

| Safety Report ID | Owner |
|---|---|
| EU-EC-001 | A |
| EU-EC-002 | B |
| EU-EC-003 | A |

In this example, EV7.1 returns all ICSRs that match the query specifications and which are flagged with the ownership of organisation 'A' and 'B' as NCA users have access to all data.

## E.2 Case based security

In EV7.1, MAHs and applicants cannot access other senders' ICSRs even when those ICSRs share the same worldwide unique case identifier.

This has been implemented to enhance the EV7.1 security taking into consideration the important confidentiality aspects related to the implementation of the EVCT-ICSRs transmissions.

In EV7.1 ICSRs, sent by different organisations sharing the same worldwide case identifier, are grouped together.

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 EV7.1 (sender based security).

Currently the system tracks the most recent information about the case with the status = 'Case Report' [See Chapter 9-ICSR Classification].

EV7.1 tracks the status = 'Case Report' for each MAH or applicant that sent the ICSRs.

EV7.1 tracks also the status = 'Case Report' for the entire set of ICSRs.

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

EV7.1 sends an alert to the EMEA Duplicate Management Administrator describing that a potential duplicate has been detected.

In case there may be differences in the content of the ICSRs, the EMEA duplicate Reports Administrator EMEA Duplicate Management Administrator will follow up with the initial senders how to manage these potential duplicates in EV7.1.

**The following example will describe a possible scenario:**

A MAH 'A' has sent a Safety Message containing an ICSR '1' to EV7.1. The ICSR stored in EV7.1 is marked with the ownership 'A' and is classified with the status = 'Case Report'.

If a new Safety Message arrives in the EV7.1 from the MAH 'C' and contains an ICSR '2' with the same data element *authoritynumb* (ICH E2B(R2) A.1.10.1) or *companynumb* (ICH E2B(R2) A.1.10.2), the ICSR is classified again with the status = 'Case Report'.

The system alerts the EMEA 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 identifier entered in the data element *authoritynumb* (ICH E2B(R2) A.1.10.1) or *companynumb* (ICH E2B(R2) A.1.10.2).

Both ICSRs (case report and replaced report) will be visible when a NCA performs a query in EV7.1 (See Table 16).

In the same query, the ICSR with the most recent information sent by the MAH (sender base security) will be reflected in Tables 14 and 15.

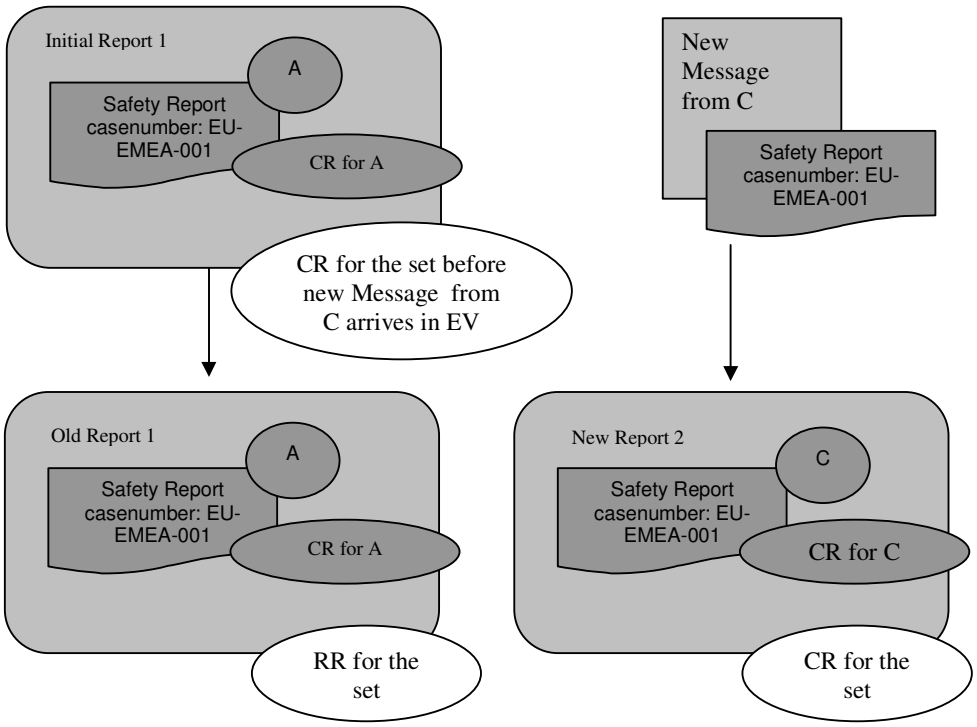


Figure 12 (CR= Case Report; RR= Replaced Report)

As a consequence, from a user right perspective, EV7.1 applies the case based security filter as presented in Figure 12. For a user belonging to MAH 'A' the query result is presented in the following table:

Table 14

| Safety Report ID | Owner | Status |
|---|---|---|
| EU-EMEA-001 | A | Case Report |

The same query would return as a result for a user belonging to MAH 'C' the following output:

Table 15

| Safety Report ID | Owner | Status |
|---|---|---|
| EU-EMEA-001 | C | Case Report |

Instead the same query would return for a user, belonging to a NCA, the output presented in the following table:

Table 16

| Safety Report ID | Owner | Status |
|---|---|---|
| EU-EMEA-001 | C | Case Report |
| EU-EMEA-001 | A | Replaced Report |

Sponsors of clinical trials conducted in the EEA do currently have no access to the ICSRs submitted to the EVCTM.

## Appendix F: Policy on Pharmaceutical Form Lookup List

EV7.1 is using as 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 the EMEA and each release will be published on the EudraVigilance website.

The lookup provides the information presented in the following example:

Table 17

| pharmaceuticalformcode | English | noncurrent | New |
|---|---|---|---|
| 207 | Soft Capsule | Yes | |
| 281 | Gel of Injection | | Yes |
| 294 | Collar | | Yes |

**Pharmaceuticalformcode:** The field contains the code of the corresponding pharmaceutical form term.

**English:** The English term of the pharmaceutical form is provided.

**Noncurrent:** The field non-current is set to 'Yes' when a new release of the European Pharmacopoeia contains a term that was present in an older version and should no longer be used.

**New**: The field 'New' is set to 'Yes' when a new release of the European Pharmacopoeia contains a new term not present in the previous edition.

When a new version of the pharmaceutical form lookup 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 Pharmaceutical Form lookup 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 Pharmaceutical Form list is published on the EudraVigilance website.

## Appendix G: Reference to the 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).

## Appendix H: Table of Changes

Table 18

| | |
|---|---|
| 25-Apr-2003 | 1. First release of the Technical document for consultation |
| 14-Aug-2003 | 1. The checks on the presence of the fields Reaction Gestation Period and Reaction Gestation Unit has been removed<br>2. It has been clarified that the drug recurraction [B.4.k.18.1b] field is mandatory within its section. The section drugrecurrence [B.4.k.18] is instead optional<br>3. 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]<br>4. 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].<br>5. 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.<br>6. A check has been added to the reacurreaction [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]<br>7. 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]<br>8. A policy for the update of the pharmaceutical form [Appendix H] has been defined.<br>9. An appendix has been added to the technical document providing the list of the changes that have been introducted to the document. [Appendix J] |
| 29-Apr-2004 | 1. Introduction has been updated introducing the reference to the transmission in the two EudraVigilance modules (CT-Module and PM-Module) (Chapter 1).<br>2. The General ICH Safety Message Flow makes now reference to the EV7.1 organisation identifiers used for EVCT and EVPM transmissions (Chapter 5).<br>3. Appendix A now specifies the business rules applicable for EVCT and EVPM transmissions.<br>4. Appendix 7 defines the endorsement of the ICH standards in EV7.1, replacing the previous EV6 version. The chapter has been updated with the business rules for the EVCTM and EVPM.<br>5. Appendix E defines the differences between the new version of message processing in EV7.1 and the replaced version EV6. The reference to the new business rules for EVPM and EVCTM is also included.<br>6. Appendix F has been updated in order to include the investigational medicinal products and to describe how the mapping mechanism changes in EV7.1.<br>7. Appendix G has been updated taking into account the new visibility rules in EV7.1. Reference to the duplicate detection process has been included. |

| | |
|---|---|
| 28-Jan-2008 | 1. New mandatory data elements have been added in Appendix A, B and C. Failure to populating these data elements generates an error message:<br>• ICH E2B(R2) A.1.1 *primarysourcecountry*<br>• ICH E2B(R2) A.1.5.1 *serious*<br>• ICH E2B(R2) A.1.5.2 *seriousness*<br>• ICH E2B(R2) A.2.1.4 *qualification*<br>• ICH E2B(R2) B.2.i.8 *reactionoutcome*<br>• ICH E2B(R2) B.4.k.1 *drugcharacterisation*<br>• ICH E2B(R2) B.4.k.2.2 *activesubstancename* (mandatory if value in data element *drugcharacterisation* (ICH E2B(R2) B.4.k.1) is '1' (suspect) or '3' (interacting)<br><br>2. New validation rules have been added in Appendix A, B and C. Failure to the validation generates an error message:<br>• If ICH E2B(R2) A.1.5.2 *seriousness* not empty, ICH E2B(R2) A.1.5.1 *serious* should be '1' (Yes)<br>• If ICH E2B(R2) A.1.5.1 *serious* value is '1' (Yes), at least one seriousness value should be '1' (Yes)<br>• The country code in ICH E2B(R2) A.1.10.1 *authoritynumb* and ICH E2B(R2) A.1.10.2 company*numb* should be a valid ISO3166 country code<br>• All reported country names should be valid ISO3166 country codes (except in ICH E(2B) B.5 section 'Narrative case summary and further information')<br>• If populated,<br>patient's and/or parent's age should be < 150 years<br>patient's and/or parent's weight should be < 650 Kg<br>patient's and/or parent's height should be < 250 cm<br>• For ICSRs submitted to the EVPM, if ICH E2B(R2) B.2.i.8 *reactionoutcome* is '5' (Fatal) for at least one reaction then ICH E2B(R2) A.1.5.1 *serious* value should be '1' (Yes) and A.1.5.2 *seriousnessdeath* value should be '1' (Yes)<br>• For ICSRs submitted to the EVMPD, if ICH E2B(R2) A.1.5.1 *serious* value is '1' (Yes) and A.1.5.2 *seriousnessdeath* value is '1' (Yes), then ICH E2B(R2) B.2.i.8 *reactionoutcome* should be '5' (Fatal) for at least one reaction<br>• At least one of ICH E2B(R2) B.4.k.1 *drugcharacterisation* value should be '1' (Suspect) or '3' (Interacting)<br>• All dates (including imprecise dates) should not be in the future.<br>• All dates except ICH E2B(R2) M.1.7b *messagedate* and ICH E2B(R2) A.1.3b *transmissiondate* should be inferior or equal to ICH E2B(R2) A.1.7b *receiptdate*<br>• All start dates should be inferior or equal to corresponding end dates<br>• For any transmission to the EVCTM, ICH E2B(R2) A.2.3.1 *studyname* should contain:<br>a) For SUSARs originating in the EEA:<br>- 'Valid Eudract Number#Study name'when ICH E2B(R2) A.1.1 *primarysourcecountry* and ICH E2B(R2) A.1.2 *occurcountry* are EEAcountries ,<br>b) For SUSARs originating outside the EEA:<br>- 'Valid Eudract Number#Study name' <u>or</u> 'Valid Development |

| | |
|---|---|
| | Medicinal Product EV Code#Study name' when ICH E2B(R2) A.1.1 *primarysourcecountry* and ICH E2B(R2) A.1.2 *occurcountry* are non-EEA countries<br>• For ICSRs sent to the EVPM, when the value of ICH E2B(R2) A.1.4 *reporttype* is '2' (report from study), the element ICH E2B(R2)A.2.3.3 *observestudytype* should not be NULL and the accepted values are '2' (individual patient use) or '3' (other studies). When the value of ICH E2B(R2)A.2.3.3 *observestudytype* is '2' (individual patient use) or '3' (other studies), the accepted value for ICH E2B(R2) A.1.4 *reporttype* is '2' (report from study)<br>• The data element *medicallyconfirm* (ICH E2B(R2) A.1.14) should be populated if the **INITIAL** Case Report has been reported by a non-health professional<br>•In the INITIAL Case Report, the ICH E2B(R2) A.1.14 data element should not be empty if the value reported in the data element *qualification* (ICH E2B(R2) A.2.1.4) is '4' (lawyer) or '5' (consumer or a non-health professional)<br>•In the INITIAL Case Report, the ICH E2B(R2) A.1.14 data element should be empty if the value reported in the data element *qualification* (ICH E2B(R2) A.2.1.4) is '1' (physician), '2' (pharmacist) or '3' (other health professional)<br>•In the subsequent FOLLOW-UP Case Report, the value of the data element *medicallyconfirm* (ICH E2B(R2) A.1.14) should be 'yes' only if the additional information has been reported by a health professional and 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 is '1' (physician), '2' (pharmacist) or '3' (other health professional)<br>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 have been added (Appendix D) |

## Appendix I: Terms in relation to electronic exchange of safety information

**Acknowledgement message (ICSRACK)**

An 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 (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**

The procedure by which on receipt of the Safety Message/Medicinal Product Report Message the syntax and semantics are checked.

**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 a clinical trial, which does not have a marketing authorisation in the EEA, and to which special confidentiality arrangements need to be applied.

**Development Substance**

Any substance under investigation in a 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 (DBMS)**

The pharmacovigilance database defined in Community legislation.

**EudraVigilance gateway**

The data-processing network as defined in the Community legislation that provides a single point of contact between MAHs, Applicants, sponsors and NCAs in the EEA. 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.

**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 reaction(s)/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 a 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 (EVMPD). 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.

**Medicinal product report transaction**

The complete set of actions in the electronic reporting of Medicinal Product Messages, which routinely includes the following:

- Creation of a Medicinal Product Report Message
- Transmission of the Medicinal Product Report Message to the Report Receiver
- On receipt of the Medicinal Product Report Message by the Receiver's Gateway return of an Message Disposition Notification (MDN)
- This MDN will be referred to as MPR-MDN
- The MPR-MDN is received and stored by the Report Sender to document the success of the Medicinal Product Report Message transmission
- The Medicinal Product Report Message is subjected to the Acknowledgement of Receipt
- procedure by the Report Receiver
- The Acknowledgement Message is created
- The Acknowledgement Message is returned to the Report Sender (technically the Report
- Receiver is a Message Sender for this part of the transaction)
- On receipt of the Acknowledgement Message by the Report Sender's Gateway return of an MDN
- This MDN is referred to as MPRACK-MDN
- The MPRACK-MDN is received and stored by the Report Receiver to document the successful transmission of the Acknowledgement Message
- The Acknowledgement Message is evaluated to document the success of the Report 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 Gatewayto-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 postauthorisation 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
- MAHs in the EEA
- Applicants
- Sponsors 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 these Guidelines is an EDI Partner. The Receiver is also the intended recipient of the transmission of a Medicinal Product Report Message, which for the purpose of these Guidelines is an EDI Partner being the Agency.

**Report sender**

Person or entity creating a Safety Message as EDI Message in order to submit a ICSR, which for the purpose of these Guidelines is an EDI Partner. 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 these Guidelines is an EDI Partner being an Applicant, a MAH or a sponsor.

**Report transaction**

The complete set of actions in the electronic reporting of Safety Messages to comply with regulatory requirements which routinely includes the following:

- Creation of a Safety Message
- Transmission of the Safety Message to the Report Receiver
- On receipt of the Safety Message by the Receiver's Gateway return of an MDN
- This MDN will be referred to as ICSR-MDN
- The ICSR-MDN is received and stored by the Report Sender to document the success of the Safety Message transmission
- The Safety Message is subjected to the Acknowledgement of Receipt procedure by the Report Receiver
- The Acknowledgement Message is created

- The Acknowledgement Message is returned to the Report Sender (technically the Report
- Receiver is a Message Sender for this part of the transaction)
- On receipt of the Acknowledgement Message by the Report Sender's Gateway return of an MDN
- This MDN is referred to as ICSRACK-MDN
- The ICSRACK-MDN is received and stored by the Report Receiver to document the
- successful transmission of the Acknowledgement Message
- The Acknowledgement Message is evaluated to document the success of the Report Transaction.

**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 ICSRs 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.

**Sponsor**

An individual, company, institution or organisation, which takes responsibility for the initiation, management and/or financing of a clinical trial (Art 2(e) of Directive 2001/20/EC).

**Standard generalized 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.