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NOTE FOR GUIDANCE

EUDRAVIGILANCE HUMAN VERSION 7.0

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

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1 Introduction

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

It is an update of the document "Technical documentation – EudraVigilance version 6.0 – Processing of Safety Messages and Individual Case Safety Reports (ICSRs)".

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

1. **EudraVigilance Post-Marketing Module**: related to ICSRs that need to be reported according to Regulation (EC) No. 726/2004, Directive 2004/27/EC and taking into account Volume 9 of the 'Rules Governing Medicinal Products in the European Union'. The Safety Reports sent to this module will be referred to in this document as EVPM-ICSRs (EudraVigilance Post Marketing Individual Case Safety Reports).
2. **EudraVigilance Clinical Trial Module**: related to ICSRS that need to be reported in accordance with Directive 2001/20/EC and the "*Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance – Clinical Trial Module-ENTR/CT 4 Revision 1)*" as published in April 2004. The Safety Reports sent to this module will be referred to in this document as EVCT-ICSRs (EudraVigilance Clinical Trial Individual Case Safety Reports).

The implementation of the two modules has required the introduction of new validation rules to be applied when the ICSRs[2] transmitted to EudraVigilance are processed.

The new validation rules are applicable as of 1 May 2004, with the release of the new EudraVigilance version 7.0 (EV7) message processing part.

The document is addressed to all parties, which are going to exchange Safety Messages and ICSRs with EV7.

The following aspects are outlined in detail:

- The generation of a valid ICH Safety Message (Chapter 2)
- Requirements for the correct loading of ICH Safety Messages in EV7 (Chapter 3)
- The General ICH Safety Message Flow (Chapter 4)
- The ICH Safety Message Flow in EV7 (Chapter 5)
- Safety Messages and ICSRs (Chapter 6)
- The ICH Acknowledgement Message (Chapter 7)
- ICSR Classification (Chapter 8)

The document describes, which aspects refer specifically to the EVPM-ICSR transmissions or the EVCT-ICSR transmissions and which apply to both.

In the appendixes of this document, a detailed description of the complete list of validation checks performed by EV7, is provided.

The endorsement of the ICH standards within EV7 are presented in Appendix D and potential improvements in EV7 versus EV6 are reflected in Appendix E. The concepts of the lookups for the medicinal product information validation and the EudraVigilance data security are summarised in Appendix F and G.

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

This document updates and replaces the business rules and validations as described in the Note for Guidance Regulatory Electronic Transmission of Individual Case Safety Reports (ICSRs) in Pharmacovigilance (EMEA/H/31387/01/FINAL).

2 Generating a Valid ICH Safety Message

This chapter describes the process of generating a valid ICH ICSR message compliant with the ICH standards, which is a prerequisite for each party to successfully exchange Safety Messages with EV. The complete reference documentation (Electronic Transmission of Individual Case Safety Report Message Specification version 2.3 (ICH ICSR DTD Version 2.1) is available at the following website: http://eudravigilance.emea.eu.int

2.1 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 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 eXtensible Markup Language *(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 must 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 in UTF-16 for language compatibility.

The ICH ICSR Safety Message must 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 ICH ICSR Safety Message must include the following DTD (Document Type Definition) reference DTD version 2.1:
<!DOCTYPE ichicsr SYSTEM "http://ers.emea.eu.int/dtd/icsr21xml.dtd">

The Acknowledgment Message must include at the message level the xml header and the dtd specification.
<?xml version=”1.0” encoding=”UTF-16”?>
<!DOCTYPE ichicsrack SYSTEM "http://ers.emea.eu.int/dtd/ichicsrack11xml.dtd">

There are two levels of conformance in the XML specifications:

Valid and well formed.

A **well-formed** message is an XML document that conforms to the structural rules of XML:

- The first line must be the XML document declaration as specified above;
- The document must contain at least one element (or tag);
- Every starting tag must 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.

A valid XML file is one, which has a DTD reference and conforms to the DTD.

The DTD (Document Type Definition) 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 **must** 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/.

3 Requirements for the Correct Loading of ICH Safety Messages in EV7

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

A Safety Message, to be successfully loaded in EV7, must be conform to the ICH ICSR standards (ICH DTD) and must respect the business rules (Appendix A).

4 The General ICH Safety Message Flow

This chapter describes the Safety Message exchange between all relevant parties involved in pharmacovigilance in the European Economic Area (EEA) with EV7. In order to transport a Safety Message to the correct receiver it is required to correctly specify the Message Sender Identifier (M.1.5) and the Message Receiver Identifier (M.1.6).

The Message Sender Identifier (M.1.5) must be the sender's own organisation identifier (organisation ID) and should be reported also in the fields company or regulatory authority name (A.3.1.2) in each Safety Report (ICSR) attached to the Safety Message.

Both, the Message Sender Identifier (M.1.5) and the Message Receiver Identifier (M.1.6) must correspond to the organization 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) or other registered parties (EudraVigilance community).

The list of all possible parties refers to Competent Authorities (CAs), Marketing Authorization Holders (MAHs), Applicants for a marketing authorisation and Sponsors of Clinical Trials in the EEA.

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 CA) and another party (e.g. 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:

1. ***Reporting to Eudravigilance (EVPM and EVCTM)***:
    a. CAs, MAHs, Applicants and Sponsors of Clinical Trials in the EEA send Safety Messages to the EMEA. They can submit Safety Reports to the EVPM-Module and as of 1 May 2004 also to the EVCT-Module.

2. ***Re-routing via EudraVigilance***:
    a. MAHs, Applicants and Sponsors of Clinical Trials in the EEA send Safety and Acknowledgment Messages to CAs in the EEA;
    b. CAs send Safety and Acknowledgments Messages to MAHs, Applicants and Sponsors of Clinical Trials in the EEA.

Reporting to the EVPM-Module (Figure 1):

1. A CA, MAH, Applicant or Sponsor of a Clinical Trial in the EEA sends ICSR(s) in a Safety Message to EV7.
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 respectively EVTEST or EVHUMAN;
3. EV7 sends an Acknowledgement Message to confirm the receipt of the Safety Message and the ICSR(s);

The example below (Figure 1) reflects the exchange of a Safety Message including one or several ICSRs from an MAH to EV7 and from a CA to EV 7.

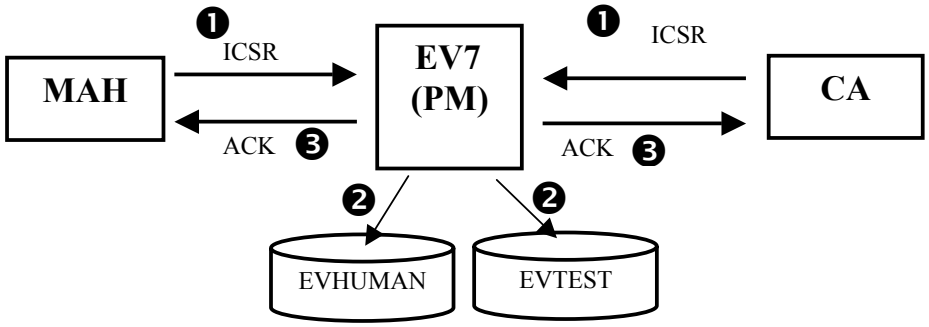


Figure 1

Reporting to the EVCT-Module (Figure 2):

1. A CA, MAH, Applicant or Sponsor of a Clinical Trial in the EEA sends ICSR(s) in a Safety Message to EV7.
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 respectively EVCTMTEST or EVCTMPROD;
3. EV7 sends an Acknowledgement Message to confirm the receipt of the Safety Message and the ICSR(s);

The example (Figure 2) reflects the exchange of a Safety Message including one or several ICSRs from an MAH to EV7 and from a CA to EV 7.

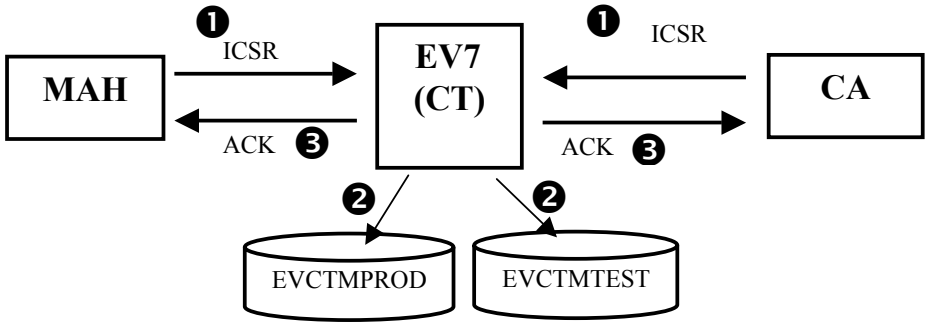


Figure 2

Re-routing via EV7:

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

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

The example (Figure 3) below reflects the exchange of a Safety Message including one or several ICSRs from an MAH to a CA via EV 7.

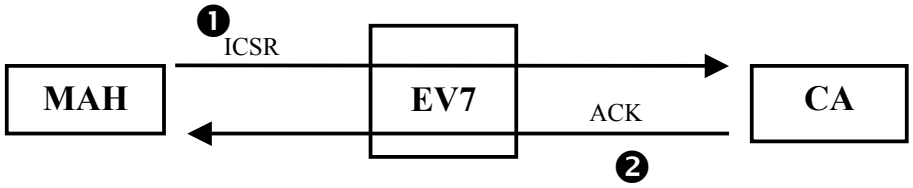


Figure 3

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

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

The example (Figure 4) below reflects the exchange of a Safety Message including one or several ICSRs from a CA to a MAH via EV 7.

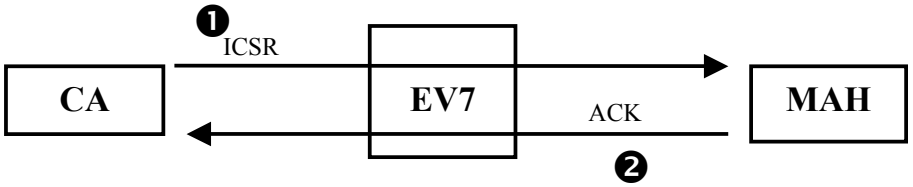


Figure 4

5 The ICH Safety Message Flow in EV7

This chapter describes the Safety Message flow in EV7 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 (please refer to chapter 2).

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

A. Inbound Parsing Validation:

1. EV7 performs a basic validation of any incoming Safety Message against the specified DTD. The sender is responsible for including the correct ICH ICSR Safety Message XML header as specified in chapter 2. In case the sender has not included the correct DTD reference header as indicated in chapter 2, the return of an Acknowledgment Message cannot be guaranteed by the receiver.
   In case of the detection of a parsing error by EV7, the following scenarios may occur:

   a. If during the parsing process of the ICH ICSR Safety Message, EV7 can detect a valid sender identifier, an Acknowledgement Message will be created and sent to the sender, listing the detected error. The Transmission Acknowledgement Code (ICH M2 A.1.6) will be reported as '03'.

   b. If during the parsing process of the ICH ICSR Safety Message, EV7 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.

   c. If the parsing process of the ICH ICSR Safety Message is successful, but EV7 cannot recognize the receiver identifier because the receiver is not registered with the EMEA, an Acknowledgement Message will be created indicating the error. The Transmission Acknowledgement Code (ICH M2 A.1.6) will be reported as '03'.

   In case the Safety Message is valid according the ICH ICSR Safety Message DTD validation, EV7 can perform one of the following actions:

   d. Re-route the Safety Message to the partner specified in the Message Receiver Identifier field (ICH M2 M.1.6). The partner must be a registered organisation in the EudraVigilance community otherwise EV7 will return a Transmission Acknowledgement Code 03.

   e. Upload the Safety Message with the Inbound Load Process into EV7 database.

B. Inbound loading process into EV7

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 the ICH-ICSR XML DTD, the message will be delivered to one of the following modules to be processed and uploaded:

a. The test environment of the EVPM if the receiver identifier is EVTEST.

b. The test environment of the EVCTM if the receiver identifier is EVCTMTEST.

c. The production environment of the EVPM if the receiver identifier is EVHUMAN.

d. The production environment of the EVCTM if the receiver identifier is EVCTMPROD.

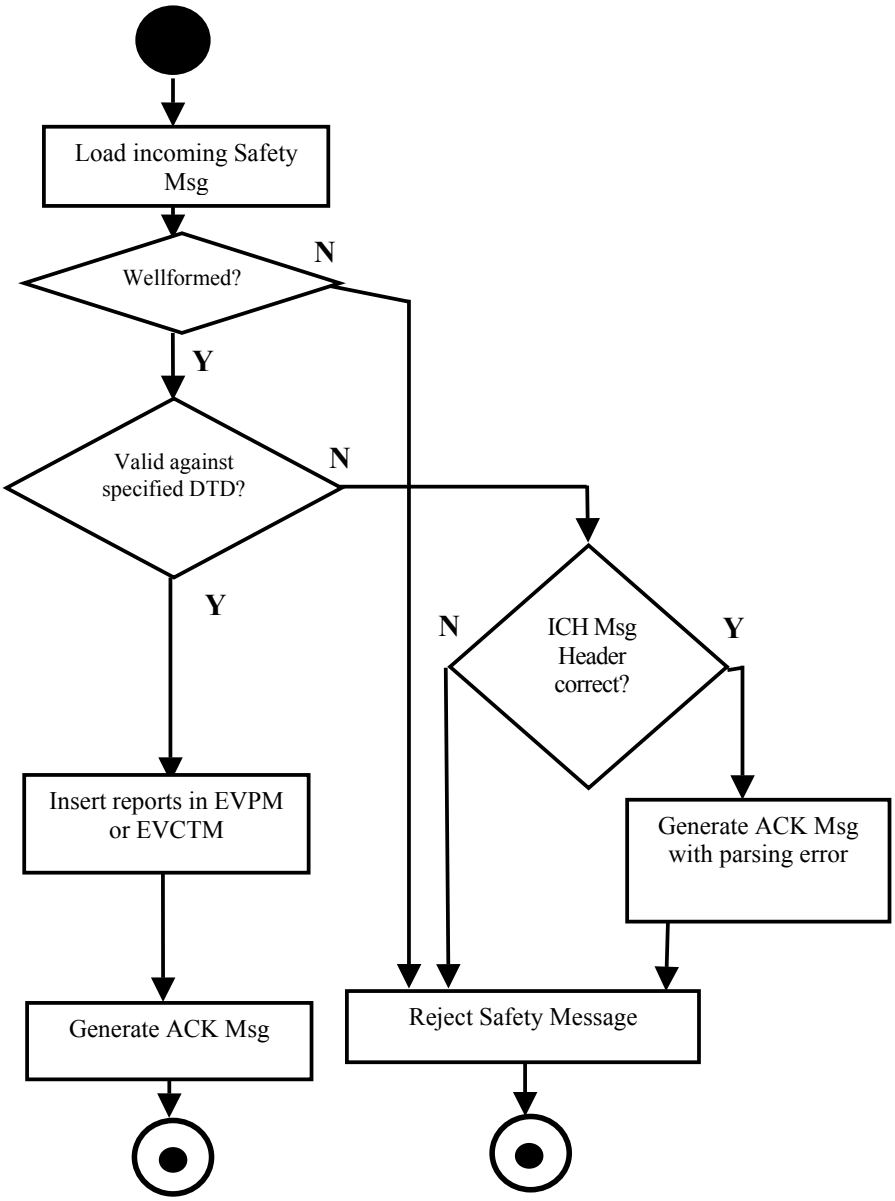


Figure 5

6 Safety Messages and 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 that must 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 2.

6.1 Message Header

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

6.1.1 Message Type

The message type contains information on the type of information being transmitted. It is specified in the M2 document (ICH M2 version 4.4.1 dated 5 February 2001). When creating an ICH ICSR message, the value of this field should be “ichicsr”.

6.1.2 Message Format Version

The message format version contains the version number of the DTD and it is specified in the M2 document (ICH M2 version 4.4.1 dated 5 February 2001).The message format version number is 2.1.

6.1.3 Message Format Release

The message format release 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.

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

The message number is a unique tracking number assigned to a specific ICH ICSR message file transmitted by the sender. This message number is unique to the sender.

6.1.5 Message Sender Identifier

This field identifies the sender of the ICSRs i.e. the organization identifier chosen by the sender in the registration process with the EMEA.

6.1.6 Message Receiver Identifier

This field identifies the intended recipient of the transmission of ICSRs i.e. the organization identifier, chosen by the recipient in the registration process with the EMEA, should be specified.

6.1.7 Message Date and Format

The message date is the date on which the ICH ICSR message was initiated.

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

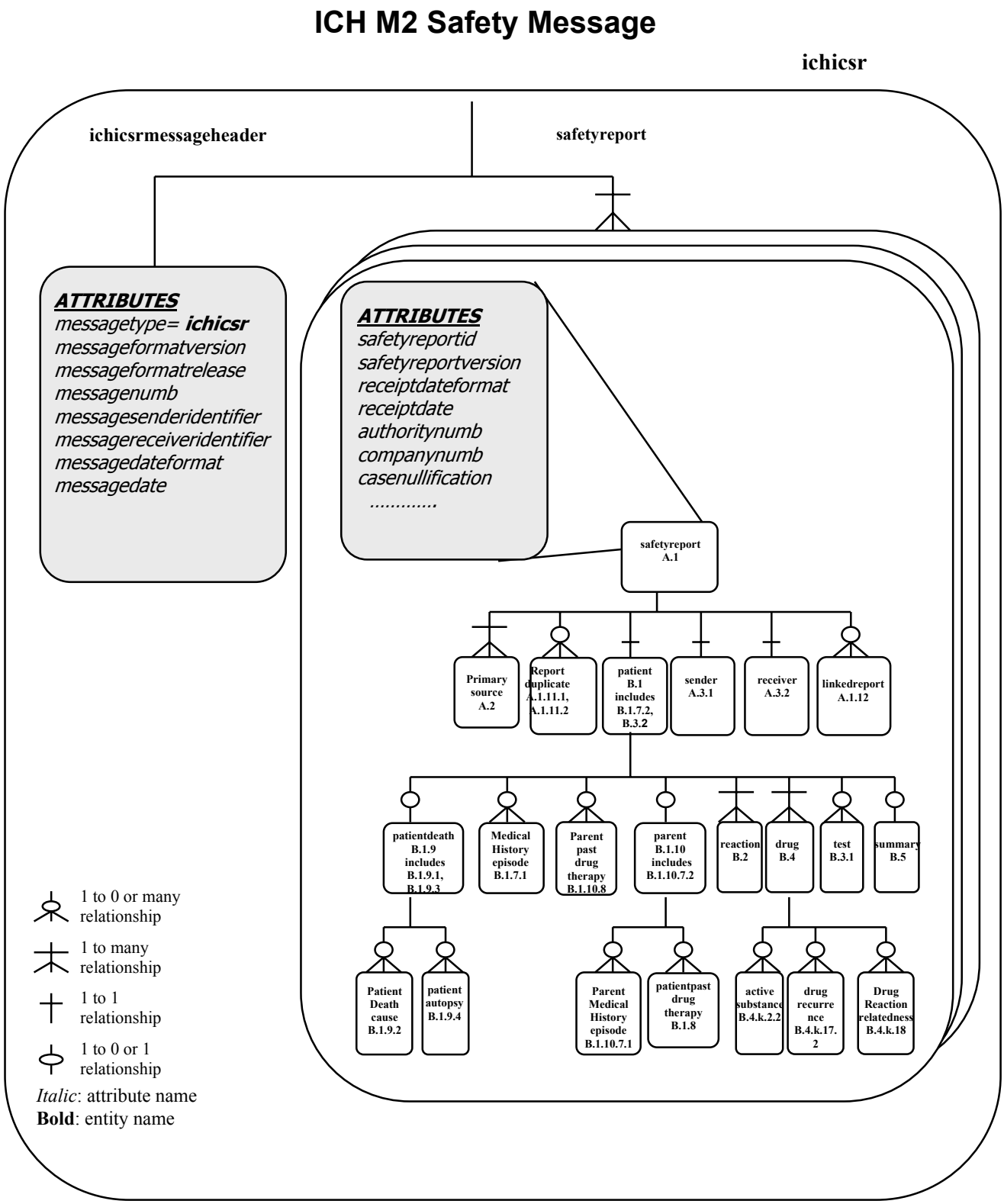


Figure 6

6.2 Safety Report

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

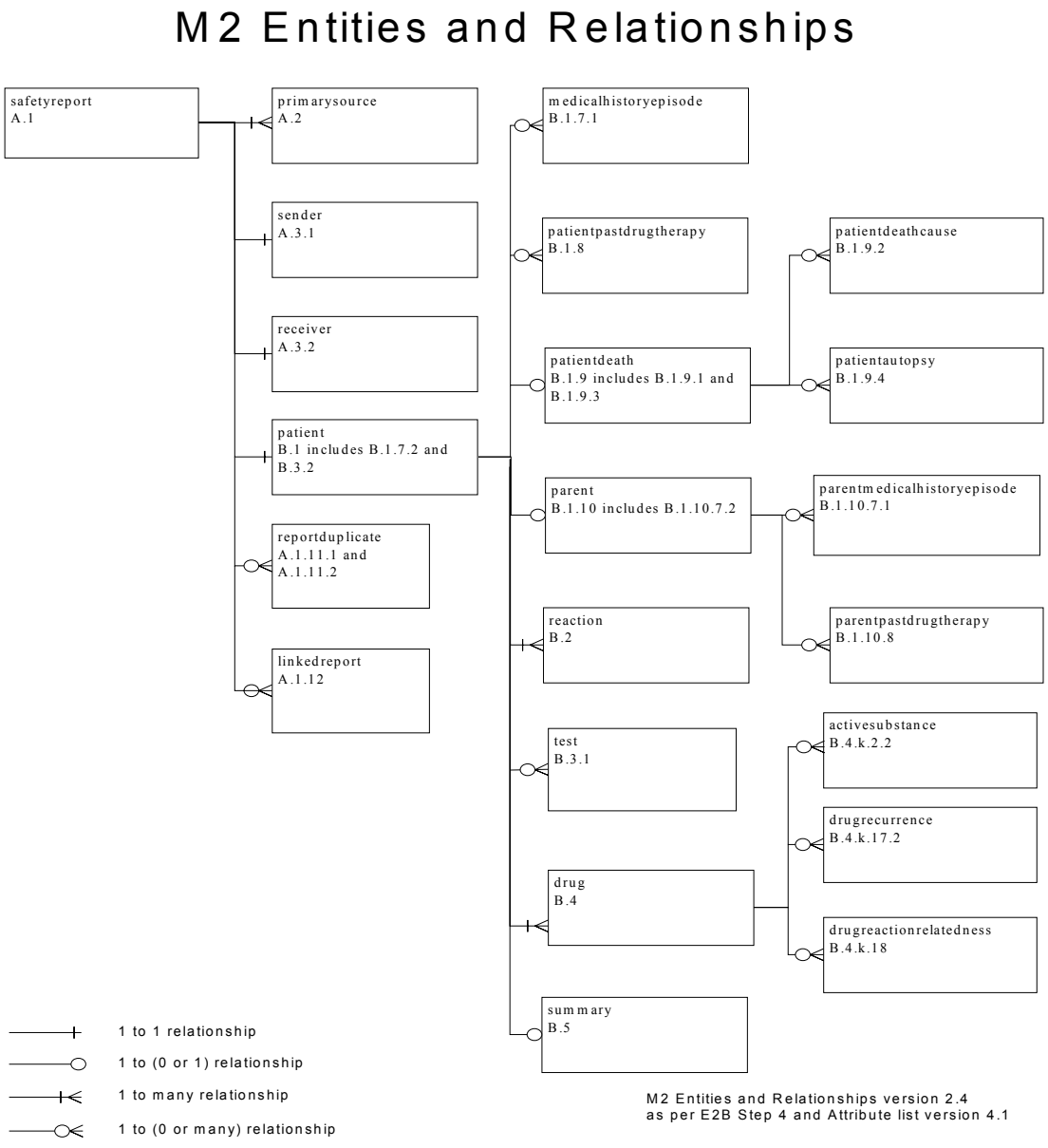


Figure 7

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

7 The Acknowledgment Message

This chapter describes the structure and field values of an Acknowledgment Message created and returned to the sender by EV7. 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 ICHICSR specifications as described in the ICH documentation Electronic Transmission of Individual Case Safety Report Message Specification version 2.3 (ICH ICSR DTD Version 2.1), available at http://eudravigilance.emea.eu.int

7.1 Acknowledgment Message Elements

An Acknowledgment Message contains the following elements (reference to the ICH document "*Electronic Transmission of Individual Case Safety Reports Message Specification Document Version 2.3", describing the fields of the acknowledgment message*)

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 02 = ICSR Error, not all reports loaded into the database, check section B 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 02=Report Not Loaded	Yes
B.1.9	Errormessagecomment	250AN		

Comment:

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.

7.2 Acknowledgment Message element description

The element description (from ICH E2B(M) "*Electronic Transmission of Individual Case Safety Reports Message Specification ICH ICSR DTD Version 2.1, Document Version 2.3" and ICH E2B(M) " 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 assigned values are the following:

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 message type contains information on the type of information being transmitted. It is specified in ESTRI recommendation 5.3. When creating an ICSR Acknowledgment SGML/XML message, the value of this field should be "ichicsrack".

- Default EV7 value is "ichicsrack"

M.1.2 Message Format Version

The message format version 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 value is "1.1"

M.1.3 Message Format Release

The message format release 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 value is "1.0"

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

The message number 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 value is "EU-EC-M-xxx-ACK" where xxx is the Local Message Number (ICH M2 A.1.2)

M.1.5 Message Sender Identifier

This field identifies the sender of the Acknowledgment, which was the receiver of the Safety Message (ICSR Attribute List A.3.2.2a).

- The sender id generated by EV7 for an Acknowledgment Message is on of the following:
    - "EVTEST" (Test environment – EVPM)
    - "EVHUMAN" (Production environment – EVPM)
    - "EVCTMTEST" (Test environment – EVCTM)
    - "EVCTMPROD" (Production environment – EVCTM)

The sender id in the Acknowledgement Message is the one originally specified in the Safety Message.

M.1.6 Message Receiver Identifier

This field identifies the receiver of the Acknowledgment, e.g. sender of the ICH ICSR message, ICSR Attribute List A.3.1.2.

The receiver id generated by EV7 for an Acknowledgment Message is the one originally specified in the Safety Message as sender id.

M.1.7a and b Message Date and Format

The message date is the date on which the Acknowledgment Message was initiated.

- Default EV7 value is "204" (messagedateformat)
- EV7 Time in CCYYMMDDHHMMSS format (messagedate)

A.1 Message Acknowledgment

This is a section header that specifies the ICH ICSR 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, Sender defined message number (unique to the sender)

The ICSR message number is a unique tracking number assigned to a specific ICH ICSR message file by the sender. This ICSR message number is unique to the sender of the ICH ICSR message.

- EV7 value is the same as for the *messagenumb (M.1.4)* of the incoming Safety Message.

A.1.2 Local Message Number

The local message number is a value assigned to the ICH ICSR message by the receiving organization. The length, data type, and value are determined by the receiving organization.

- EV7 internal unique number

A.1.3 ICSR Message Sender Identifier

This field identifies the sender of the ICSRs, e.g. ICSR Attribute List A.3.1.2, sender of case Safety Report forms.

- EV7 reports for this value the original specified *messagesenderidentifier* (ICH M.1.5) of the incoming Safety Message

A.1.4 ICSR Message Receiver Identifier

This field identifies the receiver of the ICSR reports, e.g. ICSR Attribute List A.3.2.2a, receiver identifier of the ICSR.

- EV7 reports in this field the value
    - "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.

A.1.5a and b ICSR Message Date and Format

The ICSR message date is the date on which the ICH ICSR message was initiated.

- Default EV7 value is "204" (icsrmessagedateformat)
- EV7 reports the same value for the *messagedate* (ICH M2 M.1.7b) as specified in the original incoming Safety Message (icsrmessagedate)

A.1.6 Transmission Acknowledgment Code

The transmission Acknowledgment field is a 2AN field that will inform the sender of the ICH ICSR message to either re-send the complete transmission or await Acknowledgment on individual reports.

- EV7 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 Chap 5.3 for more details)

The Parsing Error Message field is a 250 characters field that can be used to briefly describe the types of SGML/XML errors detected while parsing the file. This field is used when the value of A.1.6 is 03.

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

B.1. Report Acknowledgment

This is a section header to provide an Acknowledgment for each ICSR included in the Safety Message file. This section specifies the required elements to acknowledge the data format, data length, and data type, to ensure the information is loadable into the receiver's database (EV7). This section is a repeatable section for each report that has to be acknowledged. This section is included in the Acknowledgment Message, if the value for A.1.6 above is "02". In other words, there can be 0 to many occurrences of this section.

In order to inform the sender about the outcome of the case classification in EV7 and 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 is the number assigned by the sender to identify each ICSR.

- The field *safetyreportid* in the Acknowledgment Message is completed with the same Safety Report identifier as specified by the sender in the corresponding ICSR.

B.1.2 Safety Report Version Number

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

- The EV7 value is the same of the *safetyreportversion* of the corresponding Safety Report.

B.1.3 Local Report Number

The local report number is a value assigned to each ICSR by the receiving organization of the ICH ICSR message.

- EV7 reports for this field the system's internal unique number

B.1.4 Regulatory Authority's Case Report Number (E2BM: A.1.10.1).

B.1.4 is a unique identifier that is equivalent to the national regulatory authority's case report number. It will be the same value assigned to the E2B(M) field A.1.10.1.

- The EV7 value is the same as the *authoritynumb* (A.1.10.1) of the corresponding Safety Report field.

B.1.5 Other Sender's Case Report Number (E2BM: A.1.10.2)

B.1.5 is a unique identifier assigned by a sender which is the same as the value assigned to the E2B(M) field A.1.10.2. As the E2B(M) Step 4 document version 4.4 specifies, senders should ensure a single international number to facilitate the unique identification of a report that may have been sent to several receivers and subject to multiple re-transmissions.

- EV7 value is the same as the *companynumb* (A.1.10.2) of the corresponding Safety Report

B.1.7 a and b Date of Receipt of the Most Recent Information (E2BM: A.1.7)

This field must be used to record the date of the most recent information of the case. It is the same as the value assigned to the E2B(M) field A.1.7.

- Default EV7 value is "102" (receiptdateformat)
- EV7 value is the same value as for the *receiptdate* (A.1.7b) of the corresponding Safety Report (receiptdate)

B.1.8 Acknowledgment Code for a Report

This field is used to indicate if a report 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 text field B.1.9. The field B.1.8 is 2AN and will contain one of following values:

- EV7 value is

  01 = Report Loaded Successfully

  02 = Report Not Loaded

B.1.9 Error Message or Comment (See Chapter 5.4 for more details)

The field B.1.9 is a text field (250 characters) and it is populated by EV7 with the error and warnings, if applicable, encountered during the validation process of the Safety Report.

In order to make the sender aware of the classification results and possible warnings detected in the validation process of the Safety Message, EV7 always adds the field B.1.9 in the report Acknowledgment section of every Acknowledgment Message.

7.3 Parsingerrormessage

The Parsingerrormessage tag is included in the Acknowledgment Message only if the *transmissionacknowledgmentcode* element value is 03. The *parsingerrormessage* describes the error generated by the EV7 XML parser.

7.3.1 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 during the validation process.

Message:

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

7.4 Errormessagecomment

The field errormessagecomment appears in the section *reportacknowledgment,* which is reported as often as the number of the Safety Reports included in the Safety Message.

Following the ICH specification, the *reportacknowledgment* section should be added to the Acknowledgment Message only if the *reportacknowledgmentcode* value is 02. In order to make the sender aware of the report classification outcome, EV7 always includes this field.

- If the *reportacknowledgmentcode* value is 02 there are one or more errors and no data have been loaded successfully. In the *errormessagecomment* field EV7 describes the errors and warnings encountered during the validation process of the Safety Message. Then EV7 adds the classification outcome for the analysed Safety Report.
- If the *reportacknowledgmentcode* field is 01 the corresponding Safety Report data are loaded successfully and in the *errormessagecomment* field the classification result is presented. In case the validation process has detected

warnings, their textual description is included in the errormessagecomment field.

7.4.1 Errormessagecomment example (correct)

If a report is completely correct, without warnings, the following example shows the *errormessagecomment* as created by EV7:

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>
……
```

7.4.2 Errormessagecomment example - Error

The following example shows a possible acknowledgment for a Safety Message containing an error (the value 999 in the transmissiondateformat 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>
```

7.4.3 Errormessagecomment example - warning

The following example shows the possible Acknowledgment Message for a Safety Report loaded with warnings (The medicinal product PRODUCTEXAMPLE is not included in the EudraVigilance Medicinal Product Dictionary). If the report Acknowledgment contains warnings the corresponding Safety Report is loaded successfully in the system, in fact the Acknowledgment code is 01.

Message:

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

Acknowledgment:

```
……
    <reportacknowledgmentcode>01</reportacknowledgmentcode>
    <errormessagecomment>safety report loadedComments: 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 = Replaced Report - old:  EU-EC-M-3174 = Case
    Report </errormessagecomment>
</reportacknowledgment>
……
```

7.5 Errormessagecomment Structure

The errormessagecomment element has the following structure:

❶ Safety report loaded
❷ Comments:
  ❸ 1- In section DRUG in field medicinalproduct value: FRESH WATER
  reported Warning BUSINESSRULES - LOOKUP - CheckSub FRESH WATER must be a valid Medicinal Product;
  ……
❹ Parsing process: Report with Warnings
❺ Classification:
  ❻ new: EU-EC -3202 = Replaced Report –
  ❼ old: EU-EC -3174 = Case Report

1 –Loading Information

- Safety report loaded
- Safety report not loaded

2 – Error and Warning List (May not be present)

3 – 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

Example:

a. 2 –
b. In section SAFETYREPORT
c. For the field receiptdate
d. value: 20080405
e. reported error
f. *BUSINESSRULES - FUTUREDATE*
g. *NOT Valid Date: future date (05/04/08);*

4- Parsing Information:

- Correct Report
- Report with Warnings
- Report with Errors

5 –Classification information section (see Chapter 8)

6 –Current Report Classification

Displays the EV7 report ID and the classification outcome

7 –Old Report Classification

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

7.5.1 Error Description List

In the following chapter types of errors/warnings that may appear in an Acknowledgment Message are summarised.

7.5.1.1 Unexpected element

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

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

7.5.1.2 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.

7.5.1.3 MaxInclusive Error

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

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

7.5.1.4 MaxLength

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

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

7.5.1.5 MinInclusive Error

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

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

7.5.1.6 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.*

7.5.1.7 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.

7.5.1.8 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.

7.5.1.9 DataLength Error

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

7.5.1.10 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).

7.5.1.11 DataValid Error

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

7.5.1.12 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.

7.5.1.13 AtLeastOne Error

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

7.5.1.14 LookupMedDRALLT Error

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

7.5.1.15 LookupProducts Error

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

7.5.1.16 LookupSubstance Error

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

7.5.1.17 LookupDosageform Error

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

7.5.1.18 LookupCountryCode Error

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

7.5.1.19 LookupLanguage Error

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

7.5.1.20 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.

7.5.1.21 PreviousDate

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

7.5.1.22 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).

7.5.1.23 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.

7.5.1.24 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.

8 ICSR Classification

The classification is a process in which EV7 manages the versioning of the incoming Safety Reports. The classification rules are designed to maintain a concept in which the Safety Reports, which are classified as Case Reports describe the most recent information on a specific case of a patient. In addition, the entire history of the case reports related to a specific case is also maintained in the form of replaced reports. Further, an administrative process allows maintaining reports, which have been nullified by the original sender indicating the reasons for the cancellation of a case.

8.1 Case Classification

A report may be classified as:

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

8.1.1 Case Report

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

8.1.2 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.

8.1.3 Error Report

Error report is a report containing syntactic or semantic mistakes.

8.1.4 Nullified Report

Nullified report is a report with the case nullification set to 'yes' (ICH E2BM A.1.13) and intended to nullify a case.

8.2 Classification algorithm

This chapter presents the classification algorithm based on the field values for *nullifications*, as well as the *casenumber* and the *receiptdate*:

8.2.1 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*

8.2.2 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 report acknowledgment section.

Appendix A: Business Rules (Error Generation)

A.1 Business Rules applicable for EVPM and EVCTM (Error Generation)

This chapter summarises the complete list of the actual business rules, generating errors by EV7 in case of non-compliance.

- A Safety Message must explicitly reference DTD version 2.1 published at the EudraVigilance site (please refer to chapter 2).
- All dates must not exceed UK GMT time (+12 hours)
- <ichicsr> element **must** 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

The business rules indicated below refer to both the EVPM and EVCTM.

•	M.1.1	messagetype	Accepted Values (ICHICSR, ICSR, ichicsr, icsr)
•	M.1.2	messageformatversion	Accepted Values (2, 2.0, 2.1)
•	M.1.3	messageformatrelease	Accepted Values (0, 0.0, 1, 1.0, 2, 2.0)
•	M.1.7b	messagedate	Must be conform to M.1.7a
•	A.1.3b	transmissiondate	Must be conform to A.1.3a
•	**A.1.4**	**reporttype**	**Mandatory. See note 3**
•	A.1.6a	receivedateformat	Mandatory
•	A.1.6b	receivedate	Mandatory and must be conform to A.1.6a
•	A.1.7a	receiptdateformat	Mandatory
•	A.1.7b	receiptdate	Mandatory and must be conform to A.1.7a
•	A.1.10.1	authoritynumb	At most one between A.1.10.1 and A.1.10.2 At least one between A.1.10.1 and A.1.10.2
•	A.1.10.2	companynumb	At most one between A.1.10.1 and A.1.10.2 At least one between A.1.10.1 and A.1.10.2
•	A.2.1.1d	reporterfamilyname	At least one between 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	At least one between 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.2.1.2f	reporterpostcode	At least one between 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	At least one between 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	At least one between 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.2.2	literaturereference	At least one between 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	At least one between 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.2.3.3**	**observestudytype**	**See note 3**
•	A.3.1.4g	sendertelextension	Max Length = 10 char
•	A.3.1.4j	senderfaxextension	Max Length = 10 char
•	A.3.2.3g	receivertelextension	Max Length = 10 char
•	A.3.2.3j	receiverfaxextension	Max Length = 10 char
•	B.1.1	patientinitial	At least one between 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	At least one between 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	At least one between 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	At least one between 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	At least one between 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	At least one between 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 Must be conform to B.1.2.1a

• B.1.2.2a	patientonsetage	At least one between 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.1.2.2b	patientonsetageunit	At least one between 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.1.2.2.1a	gestationperiod	At least one between 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.1.2.3	patientagegroup	At least one between 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.1.5	patientsex	At least one between 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 and can value (1,2)
• B.1.6a	lastmenstrualdateformat	If B.1.5 = 1 (patient is male) it must be NULL
• B.1.6b	patientlastmenstrualdate	If B.1.5 = 1 (patient is male) it must be NULL and be conform to B.1.6a
• B.1.7.1a.1	patientepisodenamemeddraversion	Mandatory if B.1.7.1a.2 is not NULL and must value x.x (See Note 1)
• B.1.7.1a.2	patientepisodename	Lookup on MedDRALLTs
• B.1.7.1c	patientmedicalstartdate	Must precede B.1.7.1f and be conform to B.1.7.1b
• B.1.7.1f	patientmedicalenddate	Must follow B.1.7.1c and be conform to B.1.7.1e
• B.1.8c	patientdrugstartdate	Must precede B.1.8e and be conform to B.1.8b
• B.1.8e	patientdrugenddate	Must follow B.1.8c and be conform to B.1.8d
• B.1.8f.1	patientindicationmeddraversion	Mandatory if B.1.8f.2 is not NULL and must value x.x (See Note 1)
• B.1.8f.2	patientdrugindication	Lookup on MedDRALLTs (See Note 2)
• B.1.8g.1	patientdrgreactionmeddraversion	Mandatory if B.1.8g.2 is not NULL and must value x.x (See Note 1)
• B.1.8g.2	patientdrugreaction	Lookup on MedDRALLTs (See Note 2)
• B.1.9.1b	patientdeathdate	Must be conform to B.1.9.1a
• B.1.9.2.a	patientdeathreportmeddraversion	Mandatory if B.1.9.2.b is not NULL and must value x.x (See Note 1)
• B.1.9.2.b	patientdeathreport	Lookup on MedDRALLTs
• B.1.9.4a	patientdetermautopsmeddraversion	Mandatory if B.1.9.4b is not NULL and must value x.x (See Note 1)
• B.1.9.4b	patientdetermineautopsy	Lookup on MedDRALLTs
• B.1.10.2.1b	parentbirthdate	Must be conform to B.1.10.2.1a
• B.1.10.3a	parentlastmenstrualdateformat	If B.1.10.6= 1 (parent is male) it must be NULL
• B.1.10.3b	parentlastmenstrualdate	If B.1.10.6= 1 (parent is male) it must be NULL and conform to B.1.10.3a
• B.1.10.6	parentsex	Accepted values (1,2,9,0)
• B.1.10.7.1a.1	parentmdepisodemeddraversion	Mandatory if B.1.10.7.1a is not NULL and must value x.x (See Note 1)
• B.1.10.7.1a.2	parentmedicalepisodename	Lookup on MedDRALLTs
• B.1.10.7.1c	parentmedicalstartdate	Must precede B.1.10.7.1f and be conform to B.1.10.7.1b
• B.1.10.7.1f	parentmedicalenddate	Must follow B.1.10.7.1c and be conform to B.1.10.7.1e
• B.1.10.8c	parentdrugstartdate	Must precede B.1.10.8e and be conform to B.1.10.8b
• B.1.10.8e	parentdrugenddate	Must follow B.1.10.8c and be conform to B.1.10.8d
• B.1.10.8f.1	parentdrgindicationmeddraversion	Mandatory if B.1.10.8f.2 is not NULL and must value x.x (See Note 1)
• B.1.10.8f.2	parentdrugindication	Lookup on MedDRALLTs (See Note 2)
• B.1.10.8g.1	parentdrgreactionmeddraversion	Mandatory if B.1.10.8g.2 is not NULL and must value x.x (See Note 1)
• B.1.10.8g.2	parentdrugreaction	Lookup on MedDRALLTs (See Note 2)
• B.2.i.1.a	reactionmeddraversionllt	Mandatory if B.2.i.1.b is not NULL and must value x.x (See Note 1)
• B.2.i.1.b	reactionmeddrallt	Mandatory and Lookup on MedDRALLTs
• B.2.i.2.a	reactionmeddraversionpt	Mandatory if B.2.i.2.b is not NULL and must value x.x (See Note 1)
• B.2.i.4b	reactionstartdate	Must precede B.2.i.5b and be conform to B.2.i.4a
• B.2.i.5b	reactionenddate	Must follow B.2.i.4b and be conform to B.2.i.5a
• B.3.1b	testdate	Must be conform to B.3.1a
• B.4.k.2.1	medicinalproduct	At least one between B.4.k.2.1- B.4.k.2.2
• B.4.k.5.5	drugintervaldosagedefinition	Accepted values (801,802,803,804,805,806,807,810,811,812,813)
• B.4.k.7	drugdosageform	Lookup on Dosageforms
• B.4.k.11a	drugindicationmeddraversion	Mandatory if B.4.k.11b is not NULL and must value x.x (See Note 1)
• B.4.k.11b	drugindication	Lookup on MedDRALLTs (See Note 2)
• B.4.k.12b	drugstartdate	Must precede B.4.k.14b and be conform to B.4.k.12a
• B.4.k.14b	drugenddate	Must follow B.4.k.12b and be conform to B.4.k.14a
• B.4.k.2.2	activesubstancename	At least one between B.4.k.2.1- B.4.k.2.2
• B.4.k.17.2a	drugrecuractionmeddraversion	Mandatory if B.4.k.17.2b is not NULL and must value x.x (See Note 1)
• B.4.k.17.2b	drugrecuraction	Mandatory (if the section drugrecurrence is specified) and Lookup on MedDRALLTs
• B.4.k.18.1a	drugreactionassesmeddraversion	Mandatory if B.4.k.18.1b is not NULL and must value x.x (See Note 1)
• B.4.k.18.1b	drugreactionasses	Lookup on MedDRALLTs (See Note 2)
• B.5.3a	senderdiagnosismeddraversion	Mandatory if B.5.3b is not NULL and must value x.x (See Note 1)
• B.5.3b	senderdiagnosis	Lookup on MedDRALLTs

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

• **A.1.4**	**reporttype**	**Accepted Values (1,2,3,4). See Note 3.**
• **A.2.3.3**	**observestudytype**	**Accepted Values [2-3]. See Note 3.**

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

A.1.4	reporttype	Accepted Values (2)
A.2.3.3	observestudytype	Accepted Values (1)
A.2	primarysource	For EVCT-ICSRs the fields Studyname (A.2.3.1), sponsorstudynumb (A.2.3.2) and observestudytype need to be completed. Since these fields are contained in a repeatable section they must be specified in at least one section for each EVCT-ICSR. For this reason the EVCT-ICSRs will only be accepted by the EVCTM if these fields are reported in at least one primary source section.

NOTE:

1. The supported MedDRA versions are related to the EV 7 environment (EV7 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 MSSO. The EV7 test environment supports MedDRA versions from version 4.0 and upward. The EV7 production environment supports the previous and the most current MedDRA version. For example, in May 2004, MedDRA versions 7.0 and 6.1 are accepted in the EV7 production environment. In order to obtain the latest updates on the supported MedDRA versions in line with the official semi annual releases of MedDRA, please check the EudraVigilance website.
2. EV7 will generate a warning for certain MedDRA supported fields in E2B(M) until 31 October 2004 for a non-compliant MedDRA term. After this date the validation will generate an error. Please refer to Chapter 10 for details.
3. In the EVPM the reporttype (ICH M2 A.1.4) field becomes mandatory and the observestudytype field must contain the values (2,3) as of 31 October 2004. As of 1 May 2004 any transmissions to the EVCTM will require the reporttype (ICH M2 A.1.4) field and the observestudytype (ICH M2 A.2.3.3) to be correctly specified, in order to obtain a successful outcome of the validation of the EVCT-ICSRs (See paragraph A.2).

Appendix B: Business Rules (Warning Generation)

This chapter reflects the complete list of the actual business rules, generating warnings, by EV7.

A.3.1.4g	sendertelextension	Length up to 5 AN characters
A.3.1.4j	senderfaxextension	Length up to 5 AN characters
A.3.2.3g	receivertelextension	Length up to 5 AN characters
A.3.2.3j	receiverfaxextension	Length up to 5 AN characters
B.1.2.2b	patientonsetageunit	Mandatory if B.1.2.2a is not NULL (see note1)
B.1.2.2.1b	gestationperiodunit	Mandatory if B.1.2.2.1a is not NULL (see note1)
B.1.8a	patientdrugname	Lookup on MedicinalProducts
B.1.10.2.2b	parentageunit	Mandatory if B.1.10.2.2a is not NULL (see note1)
B.1.10.8a	parentdrugname	Lookup on MedicinalProducts
B.2.i.6b	reactiondurationunit	Mandatory if B.2.i.6a is not NULL (see note1)
B.2.i.7.1b	reactionfirsttimeunit	Mandatory if B.2.i.7.1a is not NULL (see note1)
B.2.i.7.2b	reactionlasttimeunit	Mandatory if B.2.i.7.2a is not NULL (see note1)
B.3.1c	testname	Lookup on MedDRALLTs
B.3.1e	testunit	Mandatory if B.3.1d is not NULL
B.4.k.2.1	medicinalproduct	Lookup on MedicinalProducts
B.4.k.2.2	activesubstancename	Lookup on Substances

• B.1.8f.2	patientdrugindication	Lookup on MedDRALLTs (see note 2)
• B.1.8g.2	patientdrugreaction	Lookup on MedDRALLTs (see note 2)
• B.1.10.8f.2	parentdrugindication	Lookup on MedDRALLTs (see note 2)
• B.1.10.8g.2	parentdrugreaction	Lookup on MedDRALLTs (see note 2)
• B.4.K.5.2	drugstructuredosageunit	Mandatory if B.4.k.5.1 is not NULL (see note1)
• B.4.k.5.7	drugcumulativedosageunit	Mandatory if B.4.k.5.6 is not NULL (see note1)
• B.4.k.10b	reactiongestationperiodunit	Mandatory if B.4.k.10a is not NULL (see note1)
• B.4.k.11b	drugindication	Lookup on MedDRALLTs (see note 2)
• B.4.k.13.1b	drugstartperiodunit	Mandatory if B.4.k.13.1a is not NULL (see note1)
• B.4.k.13.2b	druglastperiodunit	Mandatory if B.4.k.13.2a is not NULL (see note1)
• B.4.k.15b	drugtreatmentdurationunit	Mandatory if B.4.k.15a is not NULL (see note1)
• B.4.k.18.1b	drugreactionasses	It must be one of the values specified in reaction section in the field B.2.i.1.b (see note1)

NOTE:

1) Failure on these elements generate a warning until 31 October 2004. After this date, the validation will generate an error.
2) Failure on the MedDRA lookups generate a warning until 31 October 2004. After this date, the validation will generate an error.

Appendix C: Business Rules (Complete list)

This chapter describes the complete validation process performed by EV7.

Table Legend:

- **DATAELEMENT** Element (or session) standard code
- **NAME** Element (or session) standard name
- **MAX LEN** 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)*

DATA ELEMENT	NAME	MAX LEN	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	Must be conform to M.1.7a
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		

DATA ELEMENT	NAME	MAX LEN	TYPE	VALUES	MANDATORY	NOTES
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	Must be conform to A.1.3a
A.1.4	**Reporttype**	**1**	**N**	**[1-4]**	**Mandatory**	**See Note 8**
A.1.5.1	Serious	1	N	(1,2)		
A.1.5.2	seriousnessdeath	1	N	(1,2)		
	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	Must be conform to A.1.6a
A.1.7a	receiptdateformat	3	N	(102)	Mandatory	See Note 1
A.1.7b	receiptdate	8	N	Date	Mandatory	Must be conform to A.1.7a
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			At most one between A.1.10.1 and A.1.10.2 At least one between A.1.10.1 and A.1.10.2 See Note 3
A.1.10.2	companynumb	100	AN			At most one between A.1.10.1 and A.1.10.2 At least one between A.1.10.1 and A.1.10.2 See Note 3
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)		
	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 between 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 between 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 between 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 between 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]		At least one between 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

DATA ELEMENT	NAME	MAX LEN	TYPE	VALUES	MANDATORY	NOTES
A.2.2	literaturereference	500	AN			At least one between 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			At least one between 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, see Note 8
A.2.3.2	sponsorstudynumb	35	AN			See Note 8
A.2.3.3	**observestudytype**	**1**	**N**	**(1,2,3)**		**See Note 8**
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			
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			
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 between 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 between 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 -

DATA ELEMENT	NAME	MAX LEN	TYPE	VALUES	MANDATORY	NOTES
						B.1.2.2.1a - B.1.2.3 - B.1.5
B.1.1.1b	patientspecialistrecordnumb	20	AN			At least one between 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 between 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 between 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 between 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 Must be conform to B.1.2.1a
B.1.2.2a	patientonsetage	5	N			At least one between 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
B.1.2.2b	patientonsetageunit	3	N	[800-805]		At least one between 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 between 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			
B.1.4	patientheight	3	N			
B.1.5	patientsex	1	N	(1,2)		At least one between 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)		If B.1.5 = 1 (patient is male) it must be NULL See Note 1
B.1.6b	patientlastmenstrualdate	8	N	Date		If B.1.5 = 1 (patient is male) it must be NULL Must be conform to B.1.6a
B.1.7.2	patientmedicalhistorytext	10000	AN			
B.3.2	resultstestsprocedures	2000	AN			
B.1.7	**medicalhistoryepisode**					
B.1.7.1a.1	patientepisodenamemeddraversion	8	AN	x.x (See Note 4)		Mandatory if B.1.7.1a.2 is not NULL
B.1.7.1a.2	patientepisodename	250	AN	Lookup on MedDRALLTs		
B.1.7.1b	patientmedicalstartdateformat	3	N	(102,610,602)		See Note 1
B.1.7.1c	patientmedicalstartdate	8	N	Date		Must precede B.1.7.1f and be conform to B.1.7.1b
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		Must follow B.1.7.1c and be conform to B.1.7.1e
B.1.7.1g	patientmedicalcomment	100	AN			
B.1.8	**patientpastdrugtherapy**					
B.1.8a	patientdrugname	100	AN	Lookup on MedicinalProducts		
B.1.8b	patientdrugstartdateformat	3	N	(102,610,602)		See Note 1
B.1.8c	patientdrugstartdate	8	N	Date		Must precede B.1.8e and be conform to B.1.8b
B.1.8d	patientdrugenddateformat	3	N	(102,610,602)		See Note 1
B.1.8e	patientdrugenddate	8	N	Date		Must follow B.1.8c and be conform to B.1.8d
B.1.8f.1	patientindicationmeddraversion	8	AN	x.x (See Note 4)		Mandatory if B.1.8f.2 is not NULL
B.1.8f.2	patientdrugindication	250	AN	Lookup on MedDRALLTs		
B.1.8g.1	patientdrgreactionmeddraversion	8	AN	x.x (See Note 4)		Mandatory if B.1.8g.2 is not NULL
B.1.8g.2	patientdrugreaction	250	AN	Lookup on MedDRALLTs		
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		Must be conform to B.1.9.1a
B.1.9.3	patientautopsyyesno	1	N	(1,2,3)		
	patientdeathcause					
B.1.9.2.a	patientdeathreportmeddraversion	8	AN	x.x (See Note 4)		Mandatory if B.1.9.2.b is not NULL
B.1.9.2.b	patientdeathreport	250	AN	Lookup on MedDRALLTs		
	patientautopsy					
B.1.9.4a	patientdetermautopsmeddraversion	8	AN	x.x (See Note 4)		Mandatory if B.1.9.4b is not NULL
B.1.9.4b	patientdetermineautopsy	250	AN	Lookup on MedDRALLTs		
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		Must be conform to B.1.10.2.1a
B.1.10.2.2a	parentage	2	N			
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)		If B.1.10.6= 1 (parent is male) it must be NULL See Note 1
B.1.10.3b	parentlastmenstrualdate	8	N	Date		If B.1.10.6= 1 (parent is male) it must be NULL Must be conform to B.1.10.3a
B.1.10.4	parentweight	6	N			
B.1.10.5	parentheight	3	N			
B.1.10.6	parentsex	1	N	(1,2,9,0)		
B.1.10.7.2	parentmedicalrelevanttext	10000	AN			
B.1.10.7	**parentmedicalhistoryepisode**					
B.1.10.7.1a.1	parentmdepisodemeddraversion	8	AN	x.x (See Note 4)		Mandatory if B.1.10.7.1a is not NULL
B.1.10.7.1a.2	parentmedicalepisodename	250	AN	Lookup on MedDRALLTs		
B.1.10.7.1b	parentmedicalstartdateformat	3	N	(102,610,602)		See Note 1
B.1.10.7.1c	parentmedicalstartdate	8	N	Date		Must precede B.1.10.7.1f and be conform to B.1.10.7.1b
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		Must follow B.1.10.7.1c and be conform to B.1.10.7.1e
B.1.10.7.1g	parentmedicalcomment	100	AN			
B.1.10.8	**parentpastdrugtherapy**					
B.1.10.8a	parentdrugname	100	AN	Lookup on MedicinalProducts		
B.1.10.8b	parentdrugstartdateformat	3	N	(102,610,602)		See Note 1
B.1.10.8c	parentdrugstartdate	8	N	Date		Must precede B.1.10.8e and be conform to B.1.10.8b
B.1.10.8d	parentdrugenddateformat	3	N	(102,610,602)		See Note 1
B.1.10.8e	parentdrugenddate	8	N	Date		Must follow B.1.10.8c and be conform to B.1.10.8d
B.1.10.8f.1	parentdrgindicationmeddraversion	8	N	x.x (See Note 4)		Mandatory if B.1.10.8f.2 is not NULL
B.1.10.8f.2	parentdrugindication	250	AN	Lookup on MedDRALLTs		
B.1.10.8g.1	parentdrgreactionmeddraversion	8	AN	x.x (See Note 4)		Mandatory if B.1.10.8g.2 is not NULL
B.1.10.8g.2	parentdrugreaction	250	AN	Lookup on MedDRALLTs		
B.2	**reaction**				**Mandatory (1...∞)**	
B.2.i.1.0	primarysourcereaction	200	AN			
B.2.i.1.a	reactionmeddraversionllt	8	AN	x.x (See Note 4)		Mandatory if B.2.i.1.b is not NULL
B.2.i.1.b	reactionmeddrallt	250	AN	Lookup on MedDRALLTs	Mandatory	
B.2.i.2.a	reactionmeddraversionpt	8	AN	x.x (See Note 4)		Mandatory if B.2.i.2.b is not NULL
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		Must precede B.2.i.5b and be conform to B.2.i.4a

B.2.i.5a	reactionenddateformat	3	N	(102,203,610,602)		See Note 1
B.2.i.5b	reactionenddate	12	N	Date		Must follow B.2.i.4b and be conform to B.2.i.5a
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 is not NULL
B.2.i.8	reactionoutcome	1	N	[1-6]		
B.3	**test**					
B.3.1a	testdateformat	3	N	(102,610,602)		See Note 1
B.3.1b	testdate	8	N	Date		Must be conform with B.3.1a
B.3.1c	testname	100	AN	Lookup on MedDRALLTs		
B.3.1d	testresult	50	AN			
B.3.1e	testunit	35	AN			Mandatory if B.3.1d is not NULL (warning)
B.3.1.1	lowtestrange	50	AN			
B.3.1.2	hightestrange	50	AN			
B.3.1.3	moreinformation	1	N	(1,2)		
B.4	**drug**				**Mandatory (1...∞)**	
B.4.k.1	drugcharacterization	1	N	(1,2,3)		
B.4.k.2.1	medicinalproduct	70	AN	Lookup on MedicinalProducts		At least one between B.4.k.2.1- 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	~~AN~~			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 Dosageforms		
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 (see note1)
B.4.k.11a	drugindicationmeddraversion	8	AN	x.x (See Note 4)		Mandatory if B.4.k.11b is not NULL
B.4.k.11b	drugindication	250	AN	Lookup on MedDRALLTs		
B.4.k.12a	drugstartdateformat	3	N	(102,610,602)		See Note 1
B.4.k.12b	drugstartdate	8	N	Date		Must precede B.4.k.14b and be conform to B.4.k.12a
B.4.k.13.1a	drugstartperiod	5	N			

B.4.k.13.1b	drugstartperiodunit	3	N	[801-807]		Mandatory if B.4.k.13.1a is not NULL
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		Must follow B.4.k.12b and be conform to B.4.k.14a
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			
	activesubstance					
B.4.k.2.2	activesubstancename	100	AN	Lookup on Substances		At least one between B.4.k.2.1- B.4.k.2.2 See Note 2
	drugrecurrence				(See Note 6)	
B.4.k.17.2a	drugrecuractionmeddraversion	8	AN	x.x (See Note 4)		Mandatory if B.4.k.17.2b is not NULL
B.4.k.17.2b	drugrecuraction	250	AN	Lookup on MedDRALLTs	Mandatory (See Note 6)	
B.4.k.18	**drugreactionrelatedness**					
B.4.k.18.1a	drugreactionassesmeddra version	8	AN	x.x (See Note 4)		Mandatory if B.4.k.18.1b is not NULL
B.4.k.18.1b	drugreactionasses	250	AN	Lookup on MedDRALLTs		It must be the same as one specified in B.2.i.1.b
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 (See Note 4)		Mandatory if B.5.3b is not NULL
B.5.3b	senderdiagnosis	250	AN	Lookup on MedDRALLTs		
B.5.4	sendercomment	2000	AN			

C.1 Rules applicable to EVPM only

DATA ELEMENT	NAME	MAX LEN	TYPE	VALUES	MANDATORY	NOTES
A.1.4	Reporttype	1	N	1,2,3,4	Mandatory	
A.2.3.3	Observestudytype	1	N	2,3		

C.2 Rules applicable to the EVCTM only

DATA ELEMENT	NAME	MAX LEN	TYPE	VALUES	MANDATORY	NOTES
A.1.4	reporttype	1	N	2	Mandatory	
A.2	**primarysource**				**Mandatory (1...∞)**	For EVCT-ICSRs the fields Studyname (A.2.3.1), sponsorstudynumb (A.2.3.2) and observestudytype need to be completed. Since these fields are contained in a repeatable section they must be specified in at least one section for each EVCT-ICSR. For this reason the EVCT-ICSRs will only

DATA ELEMENT	NAME	MAX LEN	TYPE	VALUES	MANDATORY	NOTES
						be accepted by the EVCTM if these fields are reported in at least one primary source section.
A.2.3.3	observestudytype	1	N	(1)		

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" warnings**

Warning refers only to the values associated to those elements. Their presence in *medicinalproduct*, *activesubstancename* (at least one of these fields) is mandatory. In each drug section, at least one of these fields must appear, otherwise the validation performed by EV7 generates an error.

3) **"companynumb" and "authoritynumb" errors**

There must be only one value of these fields provided in each report. The system generates an error if none of these fields or both of them appear.

4) **MedDRA Versions**

The supported MedDRA versions are related to the EV 7 environment (EV7 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 MSSO. The EV7 test environment supports MedDRA versions from version 4.0 and upward. The EV7 production environment supports the previous and the most current MedDRA version. For example, in May 2004, MedDRA versions 7.0 and 6.1 are accepted in the EV7 production environment. In order to obtain the latest updates on the supported MedDRA versions in line with the official semi annual releases of MedDRA, please check the EudraVigilance website.

The validation process of the ICSRs will accept only current terms of the supported MedDRA versions.

In the EV production environment the new release of MedDRA will be implemented within 30 days of the official release date.

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 element**

The section drugrecurrence is not mandatory. The field drugrecuraction becomes mandatory if the section drugrecurrence is specified.

7) reactionmeddrapt element

The system does not check the MedDRA preferred terms reported in the reactionmeddrapt field. 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

In the EVPM the reporttype (ICH M2 A.1.4) field becomes mandatory and the observestudytype field must contain the values (2,3) as of 31 October 2004. As of 1 May 2004 any transmissions to the EVCTM will require the reporttype (ICH M2 A.1.4) field and the observestudytype (ICH M2 A.2.3.3) to be correctly specified, in order to obtain a successful outcome of the validation of the EVCT-ICSRs (See paragraph A.2).

9) patient identification

The (ICH M2 B.1.2.2.1a) patientgestation period has been added to the list of the optional fields able to identify a patient.

10) patient sex

The patient sex field (ICH M2 B.1.5) will accept only the values 1 and 2 instead of 1, 2, 9, 0. The values 0 and 9 will be accepted as warning until 31 October 2004 then the new business rule will be enforced and the message parsing will return an error.

Appendix D: Endorsement of the ICH Standards in EV7

The endorsements of the ICH standards in EV7 can be summarised as follows:

D.1 Safety Message Validation

D.1.1 EXPLICIT DTD DECLARATION

The Safety Message must contain explicitly the reference to DTD version 2.1 as published at the EudraVigilance website.

1) The following DTD reference is mandatory:

```
<?xml version="1.0" encoding="xxxxxxx"?>
<!DOCTYPE ichicsr SYSTEM "http://ers.emea.eu.int/dtd/icsr21xml.dtd">
```

2) The following DTD reference is left only for backward compatibility and it will not be possible to use it after 31 October 2004. After 31 October 2004 the only DTD reference available will be the one reported above.

```
<?xml version="1.0" encoding="xxxxxxx"?>
<!DOCTYPE ichicsr SYSTEM "http://ers.emea.eu.int/xml/icsr21xml.dtd">
```

Replace ‘xxxxxx’ with one of the XML admissible encoding (UTF-8, UTF-16, ISO-8859-1).

D.1.2 MANDATORY ELEMENTS

- *transmissiondateformat* is mandatory
- *transmissiondate* is mandatory
- *reporttype* is mandatory
- *receivedateformat* is mandatory
- *receivedate* is mandatory
- Check that when a number is specified in the following fields the corresponding measure unit is also specified. The fields are:

patientonsetage, gestationperiod, parentage, reactionduration, reactionfirsttime, reactionlasttime, testresult, drugstructuredosagenumb, drugcumulativedosagenumb, reactiongestationperiod, drugstartperiod, druglastperiod, drugtreatmentduration

- Check the presence of the MedDRA version in the following fields, if a MedDRA term is present;

  patientepisodenamemeddraversion,
  patientindicationmeddraversion,
  patientdrgreactionmeddraversion,
  patientdeathreportmeddraversion,
  patientdetermautopsmeddraversion,
  parentmdepisodemeddraversion,
  parentdrgindicationmeddraversion,
  parentdrgreactionmeddraversion,
  reactionmeddraversionllt,
  reactionmeddraversionpt,
  drugindicationmeddraversion
  drugrecuractionmeddraversion,
  drugreactionassesmeddraversion,
  senderdiagnosismeddraversion

- The ICH standard requires the following: "There are several data elements that are MedDRA controlled fields. The MedDRA version should be included for each term used. A data element for each MedDRA controlled field has been added to accommodate MedDRA version number. The ICSR attribute list and the DTD were changed to reflect these modifications".

D.1.3 LOOKUPS

- Lookup of *activesubstancename* in the EudraVigilance Medicinal Product dictionary (EVMPD) (the failure of a successful match with the EVMPD generates a warning)
- Lookup of *medicinalproduct, patientdrugname* and *parentdrugname* in the EVMPD (the failure of a successful match with the EVMPD generates a warning)
- The ICH standard requires that the fields *patientdrugindication, patientdrugreaction, parentdrugindication, parentdrugreaction, drugindication, drugreactionasses* contain a MedDRA term. EV7 will generate a warning until 31 October 2004. After this date the validation process will generate an error.

- The Safety Reports including tests should report in the testname field (B.3.1c) a valid MedDRA term. The failure of a successful match with the MedDRA lookup for the testname field will generate a warning.
- Lookup of *drugdosageform* on European Pharmacopoeia pharmaceutical forms list.

D.1.4 DATES

- Explicit check of correctness of the dates *(messagedate, transmissiondate, receivedate, receiptdate, patientbirthdate, patientlastmenstrualdate, patientmedicalstartdate, patientmedicalenddate, patientdrugstartdate, patientdrugenddate, patientdeathdate, parentbirthdate, parentlastmenstrualdate, parentmedicalstartdate, parentmedicalenddate, parentdrugstartdate, parentdrugenddate, reactionstartdate, reactionenddate, testdate, drugstartdate, drugenddate*): dates must be valid, they must conform to the corresponding date format and no date/time value must exceed the current UK GMT time plus 12 hours.
- Each start date cannot be greater than the specified end date (*patientmedicalstartdate, patientdrugstartdate, parentmedicalstartdate, parentdrugstartdate, reactionstartdate, drugstartdate*) .
- Each end date cannot be less than the start date (*patientmedicalenddate, patientdrugenddate, parentmedicalenddate, parentdrugenddate, reactionenddate, drugenddate*).

D.1.5 OTHERS

- At least one element of *authoritynumb or companynumb* must be present and only one of them must be present. "Only A.1.10.1 or A.1.10.2 should be used. No case should ever have more than one of these items completed."
- At least one element of *reporterfamilyname, reporterorganization, reporterpostcode, reportercountry, qualification, literaturereference, studyname* must be present.
- At least one element of *patientinitial, patientgpmedicalrecordnumb, patientspecialistrecordnumb, patienthospitalrecordnumb, patientinvestigationnumb, patientbirthdate, patientonsetage, patientonsetageunit, patientagegroup, patientsex* must be present.
- At least one element of *medicinalproduct* and/or *activesubstancename* must be present.
- If the patient is male *(patientsex= 1) lastmenstrualdateformat*, *patientlastmenstrualdate, reactiongestationperiod and reactiongestationperiodunit* must be null.
- If parent is male *(parentsex =1) parentlastmenstrualdateformat* and *parentlastmenstrualdate* must be null.
- *Drugrecuraction*, *drugreactionasses* must be identical to one of the MedDRA LLTs.

D.1.6 Support of EVPM-ICSRs

- reporttype with values (1, 2 , 3, 4) become mandatory.

- observestudytype changed from (1, 2, 3) to (2,3). The user cannot use the value "1".

D.1.7 Support of EV CT-ICSRs

- *reporttype* becomes mandatory. The values that can be used in this field changes from (1, 2, 3, 4) to (2).
- For EVCT-ICSRs the fields studyname (A.2.3.1), sponsorstudynumb (A.2.3.2) and observestudytype (A.2.3.3) need to be completed.

  Since these fields are contained in a repeatable section they must be specified in at least one section for each EVCT-ICSR.

  For this reason the EVCT-ICSRs will only be accepted by the EVCTM if these fields are reported in at least one primary source section.
- Values accepted for the field *observestudytype* changes from (1, 2, 3) to (1).

D.2 Max length

The following field lengths have been lengthened:

- EV7 permits the length of *sendertelextension senderfaxextension receivertelextension* and *receiverfaxextension* to be up to 10 AN characters. If the field length is grater than 5 AN the EV7 validation process will return a warning. This size will be maintained until 31 October 2004. After this date the validation process will generate an error.

The *drugdosageform* field has had the maximum field length changed from 50 to 100 AN characters in order to accept European Pharmacopoeia pharmaceutical forms. Senders can also use the EMEA codes established for the European Pharmacopoiea pharmaceutical forms. In the case that the sender wants to be compatible with the ICH standard [50 characters], the corresponding pharmaceutical form short terms should be used instead of the pharmaceutical form terms that exceed the 50 characters limit.

D.3 Extended lookups

The following lists of values have been updated:

- *messagetypelist* changed from (ichicsr) to (ICHICSR, ICSR, ichicsr, icsr). Users should use the value ichicsr in lower case format.
- *messageformatversion* changed from free text to (2, 2.0, 2.1). Users should use the value "2.1".
- *messageformatrelease* changed from free text to (0, 0.0, 1, 1.0, 2, 2.0). User should use the value "2.0".
- MedDRA version
  (*patientepisodenamemeddraversion,*
  patientindicationmeddraversion,
  patientdrgreactionmeddraversion,
  patientdeathreportmeddraversion,
  patientdetermautopsmeddraversion,
  parentmdepisodemeddraversion,
  parentdrgindicationmeddraversion,
  parentdrgreactionmeddraversion,
  reactionmeddraversionllt,
  reactionmeddraversionpt,

drugindicationmeddraversion
drugrecuractionmeddraversion,
drugreactionassesmeddraversion,
senderdiagnosismeddraversion)
Possible values changed from free text to "X.X" for the supported values, please refer to note 4 at page 39.

- *drugintervaldosagedefinition*
  possible values changed from (801,802,803,804,805,806) to (801,802,803,804,805,806,807,810,811,812,813)
- *patientsex* and *parentsex* possible values changed from (0,1,2,9) to (1,2) (fully compliant to ISO 5218)

D.4 Acknowledgment fields

In the Acknowledgment Message the following concepts need to be taken into account:

- *parsingerrormessage* does no longer contain the entire summary of the outcome of the validation process. The validation process report has been added to each report acknowledgement section in the *errormessagecomment.* In full compliance with the ICHICSR specifications this *parsingerrormessage* field will only be added if the *transmissionacknowledgmentcode* value is 03 (Safety Message not loaded) and will subsequently contain the parsing error description.
- *reportacknowledgment* is a repeatable section and will appear as many times as the number of Safety Reports contained in the original Safety Message to be acknowledged. According to the ICH ICSR DTD, the *reportacknowledgment* section should appear if the corresponding *reportacknowledgmentcode* element value is 02. However, in order to inform the sender about the outcome of the classification performed by EV7, this section will always be included in the Acknowledgement Message, even if the element value is 01.
- *errormessagecomment* contains the outcome of the validation process performed by EV7.This section may include potential warnings or errors if detected during the validation process.

Appendix E: Improvements in EV7 versus EV6

The following improvements, as part of the Safety Message processing, were introduced in EV7 compared to EV6.

E.1 Support of EVPM-ICSRs

- *reporttype becomes mandatory. The values that can be used in this field remain (1,2,3,4) and they are used together with the field observestudytype.*
- *observestudytype* changes from (1, 2, 3) to (2,3). The user cannot use the value "1".
- *patientsex* changes from (1, 2, 9, 0) to (1,2)

E.2 Support of EVCT-ICSRs

- *reporttype* become mandatory. The values that can be used in this field changes from (1, 2, 3, 4) to (2).
- For EVCT-ICSRs the fields *Studyname* (A.2.3.1), *sponsorstudynumb* (A.2.3.2) and *observestudytype* (A.2.3.3) need to be completed. Since these fields are part of the primarysource section (A.2), which is a repeatable section these fields must be specified in at least one primary source section for each EVCT-ICSR.

  For this reason the EVCT-ICSRs will only be accepted by the EVCTM, if these fields have been specified in at least one primary source section.
- Values accepted for the field *observestudytype* change from (1, 2, 3) to (1).
- *patientsex* changes from (1, 2, 9, 0) to (1,2)

Appendix F: Lookup on Medicinal Products and Substances

F.1 Definitions

EV7 performs a validation on medicinal products and substances reported in the Safety Reports. The validation of the medicinal products and substances reported in the ICH ICSR fields is performed against the EudraVigilance Medicinal Product Dictionary (EVMPD).
The definitions that apply to medicinal product and substances with regard to the EVMPD validation rules are the following:

- **Medicinal Product:**
  A Medicinal Product is defined as:
  - Any substance or combination of substances as having properties for treating or preventing disease in human beings.
  - Any substance or combination of substances, which may be used or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

- **Authorised Medicinal Product**:
  A Medicinal Product authorised either within or outside the EEA.

- **Investigational Medicinal Product**:
  An Investigational Medicinal Product is defined as 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.

- **Development Medicinal Product**:
  The development medicinal product is a medicinal product under investigation in a clinical trial in the EEA, which does not have a marketing authorisation in the EEA, and to which special confidentiality arrangements need to be applied.

- **Development Substance:**
  The developmental substance is any substance under investigation in a clinical trial in the EEA, which is not part of any authorised medicinal product.

- **Approved Substance:**
  Is any substance as defined in Community legislation (Directive 2004/27/EC), which is an ingredient of a medicinal product for which a marketing authorisation was granted within or outside the EEA.

F.2 Product Index and Scientific Database

EV7 validates the incoming ICSRs against the EVMPD.
The Product Index and the Scientific Database are two data structures, generated by entering a new medicinal product in the EVMPD. For the purpose of the Safety Report processing, the following definitions apply:

- *The Scientific Database* is a hierarchy providing a classification for all medicinal products (either with development or authorised status) registered in the EVMPD on the basis of the active ingredient(s), the concentration(s) and the pharmaceutical form(s). The hierarchy consists of the following levels:
  - *Abstract Composition*: Each Abstract Composition in the Scientific Database represents the group of medicinal products with the same active ingredient(s);
  - *Abstract Strength*: Each Abstract Strength in the Scientific Database represents the group of the medicinal products with the same active ingredient(s) and the same concentration of the active ingredient(s);
  - *Abstract Formulation*: Each Abstract Presentation in the Scientific Database represents the group of medicinal products with the same active ingredient(s) and the same pharmaceutical form(s);
  - *Abstract Presentation*: Each Abstract Composition in the Scientific Database represents the group of the medicinal products with the same active ingredient(s), the same concentration of the active ingredient(s) and the same pharmaceutical form(s).

- *The Product Index* is a reference lookup list containing reporting possibilities, which are generated when a medicinal product is entered in the EVMPD.
  - For **Authorised Medicinal Products** the reporting possibilities are generated by the splitting of the full medicinal product presentation name. Each reporting possibility is generated via the combination of the following components contained in the full presentation name:
    - Product short name
    - Product generic name
    - Product strength
    - Product pharmaceutical form
    - Product MAH name

    The combinations generated in the Product Index maintain the order of the field list specified above.
  - For **Development Medicinal Products** the reporting possibilities are created by specific identification fields provided with the development product information, such as:
    - Product code
    - Product name
    - Product other name

    These fields are never used in combination but are always entered as individual names in the Product Index.

These fields may be not always available to the sponsor and for this reason they are not mandatory in the EVMPD. In this case the Product Index entries will be generated from the scientific database.

EV7 adds to the above reference list also all the names of the Abstract Compositions, Abstract Strengths, Abstract Formulations and Abstract Presentations generated in the Scientific Database. This approach enables EV7 to have a valid list of substances and combination of substances for the mapping process of equivalent "generic products" available.

The following example illustrates the concepts of the Product Index and the Scientific Database using the information when a new authorised medicinal product is entered in the EVMPD:

Product Full Presentation Name: Antepsin Tablets 500mg
Product Short Name: Antepsin
Product Strength: 500mg
Product Pharmaceutical Form: Tablets

The Scientific Product Names for Antepsin Tablets 500 mg, generated using the active ingredient(s), the concentration(s) and the authorised pharmaceutical form(s) are as follows:

Scientific Product Names:

- Sucralfate
- Sucralfate 500mg
- Sucralfate Tablets
- Sucralfate 500mg Tablets

The Product Index Names for Antepsin Tablets 500 mg are generated when the new medicinal product information is entered into the EVMPD. The index names represent the different reporting possibilities for one and the same medicinal product taking into account the possible vagueness of the reported product information by the primary source or the sender.

Product Index Names:

- Antepsin
- Antepsin Tablets
- Antepsin 500mg
- Antepsin 500mg Tablets
- Antepsin Tablets 500 mg
- Sucralfate
- Sucralfate 500mg
- Sucralfate Tablets
- Sucralfate 500mg Tablets

The Product Index and the Scientific Product dictionary are built in a similar fashion also for development products.

The following example shows the concepts of the Product Index and scientific product database using the information when a new developmental medicinal product is entered in the EVMPD:

Product Code: CTX5132/500
Product Name: (not available)
Product Other Name: (not available)

The product contains the substance CTX5132 in the form of capsules with the strength of 500mg.

Scientific Product Names:

- CTX5132
- CTX5132 500mg
- CTX5132 capsule
- CTX5132 500mg capsule

Product Index Names:

- CTX5132/500
- CTX5132
- CTX5132 500mg
- CTX5132 capsule
- CTX5132 500mg capsule

F.3 Validation of medicinal products and substances in EVPM-ICSRs.

EV7 performs a validation on medicinal products and substances reported as field values in the Safety Reports.

The EVMPD is used as reference for the validation of the Safety Reports. The following information on medicinal products is used to validate EVPM-ICSR medicinal product and substance fields.

- All medicinal product information from authorised product.
- All reporting possibilities in the Product Index generated by authorised products.
- All authorised substances, alias and translations.

In particular the fields, on which the validations are performed, are listed below:

1. *B.4.k.2.1 medicinalproduct*: the validation procedure is performed using the algorithm described in paragraph F.6.
2. *B.4.k.2.2 activesubstancename*: the validation is done against the EVMPD substance list, including known synonyms and translations.
3. *B.1.10.8a parentdrugname*: the validation is performed using the EVMPD Product Index as a reference.
4. *B.1.8a patientdrugname*: the validation is performed using the EVMPD Product Index as a reference.

F.4 Validation of medicinal products and substances in EVCT-ICSRs

EV7 performs a validation on medicinal products and substances reported as field values in the Safety Report.

The EVMPD is used as reference for the validation of the Safety Reports. Only the following information is used to validate EVCT-ICSR medicinal product and substance fields:

- All medicinal product information from authorised medicinal products.
- All reporting possibilities in the Product Index generated by authorised products.
- All authorised substances, alias and translations.
- Only development product information from investigational medicinal products owned by the sender of the Safety Message.
- Only reporting possibilities in the Product Index generated by development products owned by the sender of the Safety Message.
- Only developmental substances, alias and translations owned by the sender of the Safety Message.

In particular the fields, on which the validations are performed, are listed below:

1. *B.4.k.2.1 medicinalproduct*: the validation procedure is performed using the using the algorithm described in chapter F.6.
2. *B.4.k.2.2 activesubstancename*: the validation is done against the EVMPD substance list, including known synonyms and translations.
3. *B.1.10.8a parentdrugname*: the validation is performed using the EVMPD Product Index as a reference.
4. *B.1.8a patientdrugname*: the validation is performed using the EVMPD Product Index as a reference.

F.5 Reporting of blinded products and Placebos

In the validation of the medicinal product information the fields:

- *B.4.k.2.1 medicinalproduct*
- *B.1.10.8a parentdrugname*
- *B.1.8a patientdrugname*

the sender can report the value “PLACEBO” in order to submit a Safety Report containing information about a placebo.

It is also possible to put as a prefix of a reported product name the text “BLINDED”. It is thus possible to report a blinded medicinal product. This possibility is outlined in the ICH E2B ICSR document.

The following example presents the possibilities specified above.

Blinded Antepsin Tablets

The EudraVigilance System will ignore the “Blinded” text. (The search for the value “BLINDED” is case insensitive).

EV7 will link the text reported with “Antepsin Tablets” and will maintain track that the product was reported as ‘blinded’ product.

The functionality to report blinded products and placebos is applicable both to the EVPM and to the EVCTM.

F.6 Medicinalproduct Field Validation

The validation that is performed in the medicinalproduct field is applicable both to the EVPM-ICSRs and to EVCT-ICSRs. It covers the following data in the Safety Report drug section:

B.4.k.2.1 medicinalproduct
B.4.k.2.2 activesubstancename
B.4.k.4.1 drugauthorizationnumb
B.4.k.4.2 drugauthorizationcountry
B.4.k.7 drugdosageform

The description of the operations performed to validate the medicinal product information using the data in the EVMPD can be summarised in the schema presented in Figure 8.

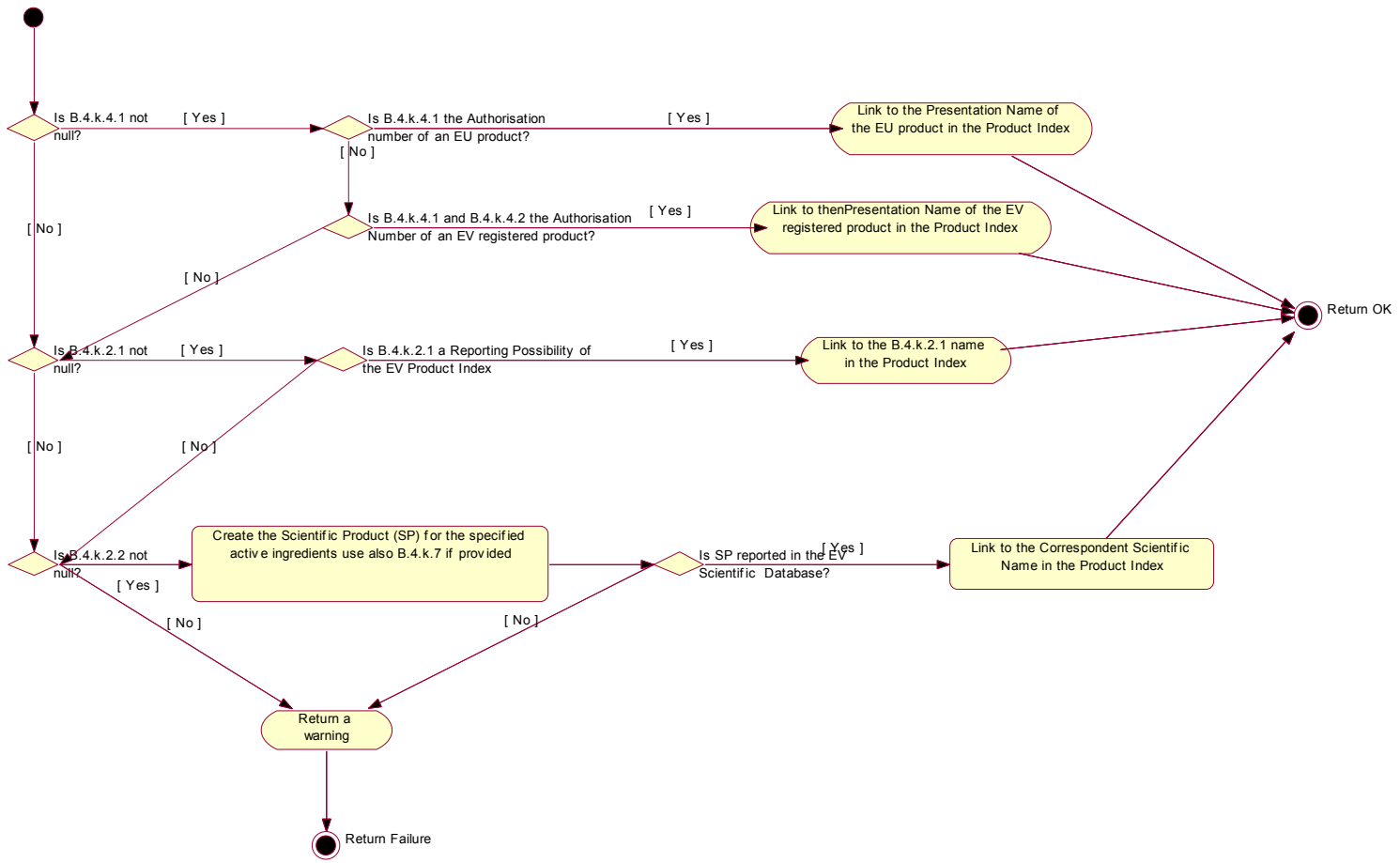
The overall validation is performed in three steps.

- The validation of the authorisation information (not applicable for development medicinal products);
- The validation of the product name using the EVMPD Product Index;
- The validation of the substance using the Scientific Database;

Each step if successful, terminates the validation process with success, retrieving the correct link to the specified product. In the case that all the three steps fail, the validation of the medicinal product fails and manual recoding has to be performed by the EMEA.

Figure 8

Medicinal Product Mapping Procedure



Appendix G: EudraVigilance Data Security

Once Safety Messages are sent to EV7 and loaded into the database they become available for query purposes to EV7 users.
EV7 users need to be individually registered with EV7 in order to be able to access the data, taking into account different levels of access rights to the data stored in EV7.
When EV7 receives a query from a user, security checks are performed, as not all Safety Reports are visible to all users. EV7 has two main policies for data security implemented with regard to access rights.

1. **Sender based security**: This is based on the Message Sender Identifier (ICH M2 M 1.5).
    a. A user of a MAH can only see the Safety Reports, that this particular MAH has submitted to EV7;
    b. A user belonging to a CA can see all Safety Reports stored in EV7, independent of the fact that the Safety Reports were submitted by a MAH, applicant or sponsor or another CA.

The following example reflects the typical behaviour of the sender-based security. EV7 flags Safety Reports with the ownership as displayed in Figure 9 (A is supposed to represent an ICSR from a MAH, B is supposed to represent an ICSR from a CA).

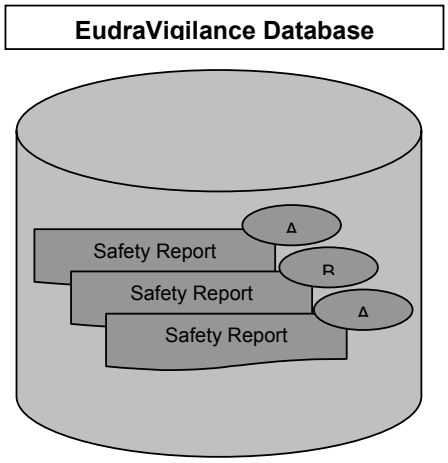


Figure 9

When a user belonging to a MAH, is accessing EV7 and is performing a query on the Safety Reports stored in EV7, the security filter will operate on the Safety Reports that were returned as a result of the query as presented below in Figure 10:

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

Figure 10

EV7 returns only those Safety Reports flagged with the ownership of organisation A, i.e. Safety Reports sent by the MAH A.

The data retrieved by the same query, considering that it is performed by a user belonging to a CA, would appear as follows (Figure 11):

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

Figure 11

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

2. **Case based security** (this was a new security policy introduced in EV6 and enhanced in EV7):

   In EV6, the ownership of Safety Reports was identified by the Message Sender Identifier (ICH M2 M 1.5) and by the case number: the worldwide unique case identifier (Regulatory Authority's Case Report Number (E2BM A.1.10.1) or Other Sender's case report number (E2BM A.1.10.2). This behaviour provides a way to identify the same case in several retransmissions also by different senders.
   EV6 was enabling users of a MAH to view Safety Reports that were originally sent by their own company as well as those Safety Reports that could have shared the same worldwide unique case identifier but were submitted by a different sender. In this instance two or more senders, from different organisations, were able to share all the information on the same case based on the same worldwide unique case identification number.

   In EV7, MAHs and applicants have no possibility anymore to access other senders' Safety Reports that share the same worldwide unique case identifier.
   This has been implemented to enhance the EV7 security taking into consideration the important confidentiality aspects related to the implementation of the EVCT-ICSRs transmissions.

   In EV7 Safety Reports, sent by different organisations, sharing the same wordwide case identifier are grouped together.

   The access to the entire set of reports will be granted only to the CAs, while the access to MAHs or applicants will be restricted to the ICSRs they have directly sent to EV7 (sender based security).

The system tracks the most recent information about the case with the status = “Case Report” (See the classification algorithm described in the paragraph 8.2).

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

EV7 tracks also the status = “Case Report” for the entire set of Safety Reports.

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

EV7 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 Safety Reports, the EMEA duplicate Reports Administrator *EMEA Duplicate Management Administrator* will follow up with the initial senders how to manage these potential duplicates in EV7.

The following example will describe a possible scenario:

A MAH (A) has sent a Safety Message containing a Safety Report to EV7. The Safety Report 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 (2) from the MAH (C) and contains a Safety Report with the same Case Number (**authoritynumb**/**companynumb** fields) 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.

In summary, the ICSR with the most recent information will receive the status = “Case Report” for the entire set of reports and will be the one shown when a CA performs a query in EV7 (Figure 12).

In the same query the ICSR with the most recent information sent by the MAH (sender base security) will be reflected.

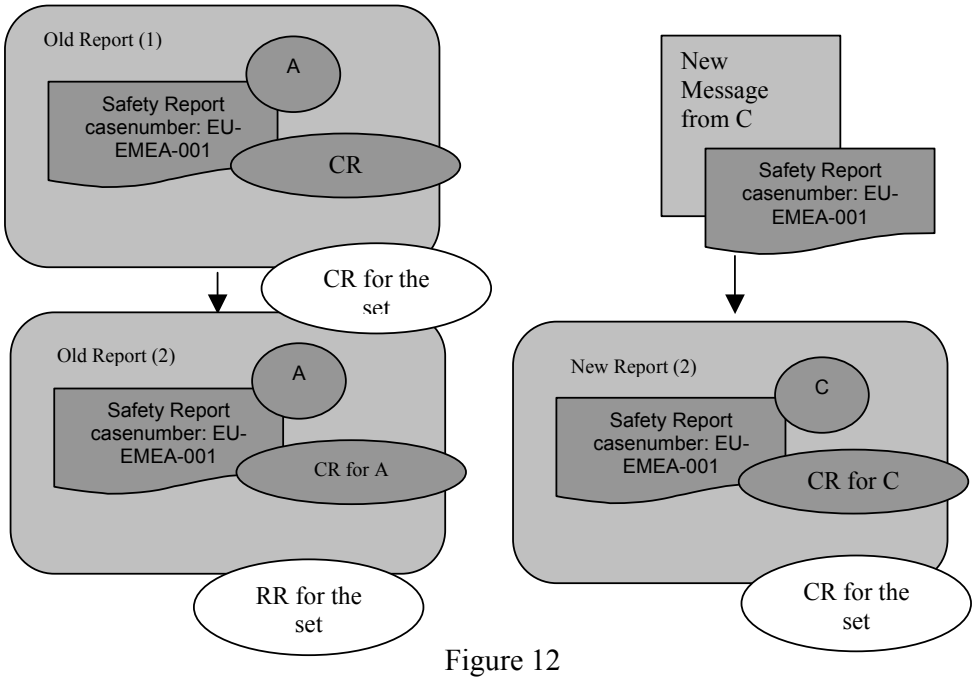


Figure 12

As a consequence, from a user right perspective, EV7 applies the case based security filter as presented in Figure 12 i.e. for a user belonging to MAH A the query result is the following (Figure 13):

Case number	Owner	Status
EU-EMEA-001	A	Case Report

Figure 13

The same query would return as a result for a user, belonging to MAH C, the following output (Figure 14):

Case number	Owner	Status
EU-EMEA-001	C	Case Report

Figure 14

Instead the same query would return as a result for a user, belonging to a CA, the following output (Figure 15):

Case number	Owner	Status
EU-EMEA-001	C	Case Report
EU-EMEA-001	A	Replaced Report

Figure 15

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

Appendix H: Update Policy on Pharmaceutical Form Lookup List

EV7 is using as a lookup list for the field drugdosageform [B.4.k.7], 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 at the EudraVigilance website.
The lookup provides the following information:

pharmaceuticalformcode	english	noncurrent	veterinary	New
207	Soft Capsule	Yes		
281	Gel of Injection			Yes
294	Collar		Yes	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.

Veterinary: The field veterinary is set to "Yes" when the term is veterinary specific.

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. Veterinary specific entries cannot be used for reporting of adverse drug reactions in humans;
3. If a term has been flagged non-current after 3 months from the date when the pharmaceutical form list is published on the EudraVigilance web site, such term cannot be used anymore for reporting in the field [B.4.k.7] of the Safety Report.

Appendix I: Reference to the EudraVigilance User Guidance

The EudraVigilance Technical Document replaces the paragraphs III.1.2 – III.1.5 of the Note for Guidance Regulatory Electronic Transmission of Individual Case Safety Reports (ICSRs) in Pharmacovigilance (Doc. Ref: EMEA/H/31387/01/FINAL).

Appendix J: Table of Changes

25 April 2003	1. First release of the Technical document for consultation
14 August 2003	1. The checks on the presence of the fields Reaction Gestation Period and Reaction Gestation Unit has been removed 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 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 must always be present otherwise a warning is generated. The warning will become an error after 30 June 2004. [Appendix B] 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]. 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. 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 must 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] 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] 8. A policy for the update of the pharmaceutical form [Appendix H] has been defined. 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] 10.
29 April 2004	1. Introduction has been updated introducing the reference to the transmission in the two EudraVigilance modules (CT-Module and PM-Module) (Chapter 1). 2. The General ICH Safety Message Flow makes now reference to the EV7 organisation identifiers used for EVCT and EVPM transmissions (Chapter 4). 3. Appendix A now specifies the business rules applicable for EVCT and EVPM transmissions.

	4. Appendix 7 defines the endorsement of the ICH standards in EV7, replacing the previous EV6 version. The chapter has been updated with the business rules for the EVCTM and EVPM. 5. Appendix E defines the differences between the new version of message processing in EV7 and the replaced version EV6. The reference to the new business rules for EVPM and EVCTM is also included. 6. Appendix F has been updated in order to include the investigational medicinal products and to describe how the mapping mechanism changes in EV7. 7. Appendix G has been updated taking into account the new visibility rules in EV7. Reference to the duplicate detection process has been included.