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

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT NOTE FOR GUIDANCE EUDRAVIGILANCE VERSION 7.1 PROCESSING OF SAFETY MESSAGES AND INDIVIDUAL CASE SAFETY REPORTS (ICSRs) (Doc. Ref. EMEA/553390/2007)

Interested party (Organisations or individuals) that commented on the draft Note for Guidance as released for consultation

	Name of Organisation or individual	Country
1	Agencia española de medicamentos y productos sanitarios (AGEMED)	ES
2	Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)	DE
3	Drug Development Consulting Services (DDCS)	LU
4	European Federation of Phamaceutical Industries and Associations (EFPIA)	EU
5	Landesamt für Gesundheit und Soziales (LAGESO)	DE
6	Lundbeck A/S (Lundbeck)	DK
7	Merck Sharp & Dohme Ltd. (MSD)	UK
8	Voisin Consulting (Voisin)	FR
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1. GENERAL COMMENTS

Organisation	General Comment	Outcome of EudraVigilance Expert Working Group review
DDCS	Why is this document named EudraVigilance Human Version 7.1 where EV-Web current version is 7.3	Document renamed as follows: Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (Doc. Ref. EMEA/H/20665/04/Final, Revision 1)
EFPIA	Overall EFPIA supports the recommendations regarding the EudraVigilance Medicinal Product Dictionary (EV MPD) and would welcome them to be implemented as in the current draft however a few issues are raised in the detailed comments. ICH M5 guideline on the identification of medicinal products is ongoing but the basic data elements agreed by the EMEA and EFPIA are respected. The cost for implementing any changes to the reporting system is high and is increasing when companies have to implement changes to meet different standards. An ICSR produced to E2B standard must be subject to the same level of validation (i.e. mandated data-tag checks) across all Regulators without the need to differentiate between them on specific data-tag.	Supportive comment. The business rules and validation processes detailed in the Note for Guidance apply to all stakeholders, which are exchanging Safety Messages and ICSRs electronically at Community level in line with Regulation (EC) No 726/2004, Directive 2001/83/EC as amended, Directive 2001/20/EC, Volume 9A and Volume 10 of the Rules Governing Medicinal Products in the European Union.
LAGESO	In following chapters of the above mentioned draft guidance you plan to submit the initials and the full birth date of the patients to the Eudravigilance Data base. Chapter A.1 Business Rules applicable to the EVPM and EVCTM (Error Generation) sub B 1.1 and B 2.1.b. (page 50) and B.1.10.2.1b (page 39) Chapter C.1 Rules applicable to the EVPM and EVCTM <<Eudravigilance Safety Messages 55339007en draft.pdf>> sub B 1.1 and B 2.1.b. (page 50) and B.1.10.2.1b (page 52) Attached you find an article about the question, whether it is legal or not (based on the german medicinal product law, the Directive 2001/20/EC and the Directive 1995/46/EC), to submit the full birth date (not the age in years) and/or the initials of "subjects" in clinical trials. I suggest contacting the European data protection supervisor http://www.edps.europa.eu/EDPSWEB/edps/lang/de/pid/1 to let him check, if	At least one of the data elements in the ICH E2B(R2) B.1 section Patient needs to be populated in order for an ICSR to be valid. The recommendations regarding the electronic transmission of ICSRs based on the principles of anonymised information are presented in Part III, Chapter 5.4 of Volume 9A. The Opinion on a Notification for Prior Checking Received from the Data Protection Officer of the European Medicines Agency ("EMEA") regarding the EudraVigilance database was published (Case 2008-402) in September 2009. The recommendations of the European Data Protection Supervisor (EDPS) will be addressed in the context of the finalisation of the EudraVigilance Access Policy.

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	these demographic data of the patients are allowed to be submitted to the Eudravigilance Data base although these identifiers are not necessary to judge the SUSAR.	
Lundbeck	Lundbeck A/S welcomes this Note for Guidance and has no comments to add to the proposed document.	Supportive comment
MSD	While the majority of the proposed changes are straightforward, some will require MAHs/Sponsors to make significant changes to their database systems and/or procedures in order to produce fully compliant E2B messages. Accordingly, if these rules become mandatory without sufficient time for such adaptation being allowed, it is highly likely that the current successful process of ICSRs submissions to Eudravigilance will be jeopardised. It is not clear from this draft if the new rules will apply to both expedited and periodic submissions – please clarify. If they do apply to both then the section on seriousness criteria may cause compliance issues due to differing US/EU definitions.	Document updated as follows: The revised business rules are relevant to all ICSRs which qualify for expedited and periodic reporting and originating within or outside the EEA. The new validation rules and mandatory ICH E2B(R2) data elements should be implemented as outlined in the detailed Implementation Plan (Doc. Ref. EMEA/665231/2008). Separate business rules apply for the retrospective population of the EudraVigilance Post Authorisation Module. They are described in Part III of Volume 9A of the Rules Governing Medicinal Products in the European Union.
Wyeth	In considering the direction provided in this version of the guidance, we recommend that EMEA consider including a section to describe the method of transitioning the reporting of on-going cases. Mores specifically, at the time that version 7.1 of EudraVigilance system goes into production, it is unclear whether the follow-up reporting of existing cases (previously submitted) will be subject to the new validation rules, or whether these new rules will apply only to the reporting new cases after the effective date. In reporting Individual Case Safety Reports to non-EEA Boards of Health, these reports are commonly submitted through the EudraVigilance system and network. We recommend that the document clarify that the handling of these non-EEA ICSRs will not be subject to the new business rules and validation steps associated with the EEA member submission.	Document updated as follows: The revised business rules are relevant to all ICSRs which qualify for expedited and periodic reporting and originating within or outside the EEA. The new validation rules and mandatory ICH E2B(R2) data elements should be implemented as outlined in the detailed Implementation Plan (Doc. Ref. EMEA/665231/2008). Separate business rules apply for the retrospective population of the EudraVigilance Post Authorisation Module. They are described in Part III of Volume 9A of the Rules Governing Medicinal Products in the European Union.

2. SPECIFIC COMMENTS ON TEXT

Page No. + paragraph No.	Organisation	Comment and Rationale	Outcome of EudraVigilance Expert Working Group review
Executive Summary, Page 3	Voisin	Comments: New validation rules generating error messages: For any transmission to the EudraVigilance Clinical Trial Module, the 'Study name' data element should contain: a) For SUSARs originating in the EEA: - 'Valid EudraCT Number#Study name', b) For SUSARs originating outside the EEA: - 'Valid EudraCT Number#Study name' or 'Valid Development Medicinal Product EV Code#Study name' Proposed change: Based on practice, it is usually difficult to include the entire protocol title in the study name field. Therefore, we suggest you to increase the number of limited characters above 100 or to provide a naming convention for the study name as example of guide.	Sentence added in Note 7 & 13 of Appendix A and C respectively: If necessary the study name should be abbreviated in the data element *studyname* (ICH E2B(R2) A.2.3.1). The entire study name can eventually be included in the data element *narrativeincludeclinical* (ICH E2B(R2) B.5.1).
Executive Summary, Page 3	Voisin	Comments: We suggest you make the unit for lab results a mandatory field, since lab results with no unit are irrelevant.	Proposed changed not accepted. Test unit is not always available from the primary source. If no test unit is reported, this proposal would require entering systematically NOS to avoid the generation of an error message.
Executive Summary, Page 3	Voisin	Comments: Previously, in the Note for Guidance EudraVigilance Human version 7.0 the qualification of the primary source reporter was not mandatory. Add the following sentence in this paragraph regarding the new validation rules generating error messages: 'Primary source qualification should be specified'.	Proposed change accepted.

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Chapter 1 Introduction, Page 7	MSD	Comments: When will EV7.1 be in place and hence these requirements become mandatory?	Stakeholders will be given a 6 months period after publication of the business rules to implement the business rules. Document updated as follows: The new validation rules and mandatory ICH E2B(R2) data elements should be implemented as outlined in the detailed Implementation Plan (Doc. Ref. EMEA/665231/2008).
Chapter 1 Introduction, Page 7	MSD	Comments: Are these proposed rules applicable also to periodic ICSR files i.e. 'psur' and 'ctasr' files. If yes, this should be stated in the document.	Sentence added: The revised business rules are relevant to all ICSRs which qualify for expedited and periodic reporting and originating within or outside the EEA.
Chapter 1 Introduction, Page 7	Voisin	Comments: The guideline defines the EudraVigilance post marketing module as follows: 1. EudraVigilance Post-Marketing Module (EVPM): related to ICSRs that need to be reported according to Regulation (EC) No. 726/2004, Directive 2004/27/EC and taking into account Volume 9A. The Safety Messages sent to this module contain spontaneous reports and reports from non-interventional trials only. The ICSRs received in this module will be referred to in this document as EVPM-ICSRs (EudraVigilance Post-authorisation Module Individual Case Safety Reports). This is not clear in this paragraph to which module the expedited safety reports occurring during the compassionate use programmes will be sent. It should be stated that this reports should be sent to this EVPM module. In addition, handling of legacy data from the Non European named and cohort compassionate use progarmmes should be addressed in this guideline.	New chapter added regarding types of reports to be sent to EVPM and EVCTM: a) The EudraVigilance Post-Authorisation Module (EVPM): related to ICSRs, which need to be reported according to Regulation (EC) No. 726/2004, Directive 2001/83/EC as amended and Volume 9A of the Rules Governing Medicinal Products in the European Union. The Safety Messages sent to this module contain spontaneous reports, reports occurring in the frame of compassionate use programmes, legacy reports and reports from non-interventional studies. The ICSRs received in this module will be referred to in this document as EVPM-ICSRs (EudraVigilance Post-authorisation Module Individual Case Safety Reports). **b)** The EudraVigilance Clinical Trial Module (EVCTM): related to ICSRs, which need to be reported in accordance with Directive 2001/20/EC and Volume 10 of the Rules Governing Medicinal

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			Products in the European Union. The Safety Messages sent to this module contain reports from interventional clinical trials only, as defined in Article 2(a) of Directive 2001/20/EC. The ICSRs received in this module will be referred to in this document as EVCT-ICSRs (EudraVigilance Clinical Trial Individual Case Safety Reports).
Chapter 3.1 Paragraph 6&7, Page 10	Wyeth	Comments: Currently the EMEA domain name is explicitly stated in the SYSTEM URL identification. Using this approach, the Marketing Authorisation Holder (MAH) must populated the ICSR with the domain name while submitting to the recipient. Post submission, if the MAH would need to access the XML ICSR, it would assume that the domain name is a valid name. If, however, the domain has been deactivated, the MAH will get an error while opening the previously submitted ICSR which now contains an expired domain name. Proposed change: Instead of using the actual domain name in the ICSR, the EMEA should provide an alias that should be populated in the ICSR. On the back end, the alias should map to the actual domain name. This would allow for the domain name to be deactivated/changed, etc. without impacting the ability of the MAH to review previously submitted ICSRs without getting an error message.	Proposed change not accepted. Proposal will affect all organisations requiring them to update their applications.
Chapter 5 ICH Safety Message Flow, Page 13	Voisin	Comments: Inside the EudraVigilance community, the possible communication scenarios are the following: Reporting to EudraVigilance (EVPM and EVCTM): a. NCAs, MAHs, Applicants and Sponsors of Clinical Trials	Proposed change not accepted. Functions of Gateway and EVWEB are misunderstood in the proposed changes.

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		send Safety Messages to the EMEA. They can submit ICSRs to the EVPM-Module and to the EVCTModule. Re-routing via EudraVigilance: a. MAHs, Applicants and Sponsors of Clinical Trials send Safety and Acknowledgment Messages to NCAs in the EEA; b. NCAs send Safety and Acknowledgments Messages to MAHs, Applicants and Sponsors of Clinical Trials. Proposed change: For clarity, we suggest that you change the order to reflect points 1 and 2 above this paragraph, and add the following text: Inside the EudraVigilance community, the possible communication scenarios are the following: Re-routing via EudraVigilance (via Gateway 7.1): a. MAHs, Applicants and Sponsors of Clinical Trials send Safety and Acknowledgment Messages to NCAs in the EEA; b. NCAs send Safety and Acknowledgments Messages to MAHs, Applicants and Sponsors of Clinical Trials. Reporting to EudraVigilance (EVPM and EVCTM to EVWEB): a. NCAs, MAHs, Applicants and Sponsors of Clinical Trials send Safety Messages to the EMEA. They can submit ICSRs to the EVPM-Module and to the EVCTModule.	
Chapter 5.1. Reporting to the EVPM-	Voisin	Comments: We suggest that you add “Applicant” in the diagram, as follows:	Proposed change accepted.

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Module, Figure 1, Page 14		MAH /Applicant (e.g. to cover changes in the risk/benefit ratio from data generated by compassionate use).	
Chapter 5.3. Re-routing via EV7.1, Figure 3, Page 15	Voisin	Comments: We suggest that you add "Applicant" in the diagram, as follows: MAH /Applicant /Sponsor	Proposed change accepted.
Chapter 5.3. Re-routing via EV7.1, Figure 4, Page 15	Voisin	Comments: We suggest that you add "Applicant" in the diagram, as follows : MAH /Applicant / Sponsor	Proposed change accepted.
Figure 5, Page 17	DDCS	Comments: Replace Incoming Safety Message by Incoming Message	Proposed change not accepted. This chapter and the corresponding figure relates to Safety Message flow for the electronic transmission of ICSRs and not to product reports.
Chapter 8. The Acknowledgment Message, Page 21	Voisin	Comments: This chapter describes the structure and the field values of an Acknowledgment Message created and returned to the sender by EV7.1. It provides the sender with the results of the outcome of the loading process and any detected errors and warnings. Proposed change: This chapter describes the structure and the field values of an Acknowledgment Message created and returned to the sender by EV7.1. It provides the sender with the results of the outcome of the loading process and, any detected errors and warnings <u>by parsing process and the updated classification status.</u>	Proposed change accepted.

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Chapter 8.1. Acknowledgment Message Elements, Table 1, line 4, column Field Value, Page 21	Voisin	Comments: In the data element M.1.2, *Messageformatversion*, the Field Value should be completed with "1.1".	Proposed change accepted.
Chapter 8.1. Acknowledgment Message Elements, Table 1, line 5, column Field Value, Page 21	Voisin	Comments: In the data element M.1.3, *Messageformatrelease*, the Field Value should be completed with"1.0"	Proposed change accepted.
Chapter 8.1. Acknowledgment Message Elements, Table 1, line 7, column Field Value, Page 21	Voisin	Comments: In the data element M.1.5, *Messagesenderidentifier*, the Field Value should be completed with the following: "- 'EVTEST' = Test environment – EVPM - 'EVHUMAN'= Production environment – EVPM - 'EVCTMTEST' = Test environment – EVCTM - 'EVCTMPROD' = Production environment – EVCTM"	Proposed change not accepted. The proposed changes are applicable for submission to EudraVigilance only whereas elements presented in Table 1 are aimed to be applicable to all systems. The specific Message Sender IDs generated by EudraVigilance are detailed in Chapter 9.2.1 in section M.1.5 Message Sender Identifier. Sentence before Table 1 replaced by 'An Acknowledgment Message created and returned to the sender contains the elements presented in Table 1, as described in the ICH M2 and ICH E2B(R2) documents.
Chapter 8.1.	Voisin	Comments:	Proposed change not accepted.

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Acknowledgment Message Elements, Table 1, line 15, column Field Value, Page 21		In the data element A.1.4, *Icsrmessagereceiveridentifier*, the Field Value should be completed with the following: "- 'EVTEST' = Test environment – EVPM - 'EVHUMAN'= Production environment – EVPM - 'EVCTMTEST' = Test environment – EVCTM - 'EVCTMPROD' = Production environment – EVCTM"	The proposed changes are applicable for submission to EudraVigilance only whereas elements presented in Table 1 are aimed to be applicable to all systems. The specific Message Receiver IDs generated by EudraVigilance are detailed in Chapter 9.2.2 in section A.1.4 ICSR Message Receiver Identifier. Sentence before Table 1 replaced by 'An Acknowledgment Message created and returned to the sender contains the elements presented in Table 1, as described in the ICH M2 and ICH E2B(R2) documents.
Chapter 8.1. Acknowledgment Message Elements, Table 1, line 19, column Mandatory, Page 21	Voisin	Comments: In the data element A.1.7, *Parsingerrormessage*, the column "Mandatory" should be completed with "Yes, if A.1.6 = 03"	Proposed change accepted.
Chapter 8.1. Acknowledgment Message Elements, Table 1, Page 21	DDCS	Comments: Data elements A.1.2, B.1.1, B.1.4 and B.1.5 should be mandatory cf. Note for Guidance EV Human Version 7.0	Proposed change partly accepted. It is unknown whether all organisations are assigning a local message number (ICH E2B(R2) A.1.2), it cannot be make mandatory. Other changes accepted.
Chapter 8.2.2. A.1 Message Acknowledg	Voisin	Comments: A.1.2 Local Message Number The value in the data element *localmessagenumb* (ICH M2	Proposed change accepted. EV local message number matches part of value in data element ICH M2 M.1.4 ('EU-EC-M-xxx-ACK').

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ment, Page 24		A.1.2) is assigned to the Safety Message by the receiving organisation. The length, data type, and value are determined by the receiving organisation. _ EV7.1 internal unique number Proposed change: We suggest that you add the following: 'A.1.2 Local Message Number The value in the data element *localmessagenumb* (ICH M2 A.1.2) is assigned to the Safety Message by the receiving organisation. The length, data type, and value are determined by the receiving organisation. _ EV7.1 internal unique number value is "EU-EC-M-xxx"as referred to in the data element messagenumb (ICH M.1.4)"	
Chapter 8.2.3. B.1 Report Acknowledgment, Page 25	Voisin	Comments: **B.1.3 Local Report Number** The local report number is a value assigned to each ICSR by the receiving organisation of the Safety Message. _ EV7.1 reports for this data element the system's internal unique number. Proposed change: A follow-up of an ICSR does not have the same local report number as the previous version of the ICSR, therefore we suggest adding the following: B.1.3 Local Report Number	Proposed change not accepted. This is a recommendation from ICH M2 document.

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		The local report number is a value assigned to each version of an ICSR by the receiving organisation of the Safety Message. _ EV7.1 reports for this data element the system's internal unique number.	
Appendix A – Section A.1 Business Rules applicable to the EVPM and EVCTM (Error Generation), Table 2, Page 35	Voisin	Comments: In the data element M.1.6, *messagereceiveridentifier*, the "Values" column should be completed with the following: "- 'EVTEST' = Test environment – EVPM - 'EVHUMAN'= Production environment – EVPM - 'EVCTMTEST' = Test environment – EVCTM - 'EVCTMPROD' = Production environment – EVCTM"	Proposed change accepted. Note added: When submitting a Safety Message to EV, the value accepted in the data element *messagereceiveridentifier* (ICH M2 M.1.5) is one of the following, depending to which module the message is addressed: - 'EVTEST' (Test environment – EVPM) - 'EVHUMAN' (Production environment – EVPM) - 'EVCTMTEST' (Test environment – EVCTM) - 'EVCTMPROD' (Production environment – EVCTM).
Appendix A – Section A.1 Business Rules applicable to the EVPM and EVCTM (Error Generation), Table 2, Page 36	DDCS	Comments: Data elements A.1.10.1 and A.1.10.2: Include in column Mandatory: 'Mandatory, one of A.1.10.1 or A.1.10.2'	Proposed change accepted.
	Voisin	Comments: In the data element A.1.10.1, *authoritynumb*, the "Notes" field should be completed with "NULL if A.1.10.2" In the data element A.1.10.2, *companynumb,* the "Notes" field should be completed with "NULL if A.1.10.1"	Proposed change partly accepted: One of A.1.10.1 or A.1.10.2 accepted.

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	DDCS	Comments: Data elements A.2.3.2 Replace 'Mandatory for transmission to EVCTM' by Mandatory for any transmission to EVCTM	Proposed change accepted.
	Voisin	Comments: Based on practice, it is usually difficult to include the entire protocol title in the study name field (ICH E2B(R2) A.2.3.1). Therefore, we suggest you to increase the number of limited characters above 100 or to provide a naming convention for the study name as example of guide.	Chapter added in Note 7 The data element *studyname* (ICH E2B(R2) A.2.3.1) is limited to 100 characters. If necessary the study name should be abbreviated in the concatenation. The entire study name can be included in the data element *narrativeincludeclinical* (ICH E2B(R2) B.5.1).
	MSD	Comments: Data elements ICH E2B(R2) A.1.5.1 and A.1.5.2: Seriousness criteria should match with ICSR seriousness. This raises an issue where the EU and US definition of serious varies, i.e. Cancer/Overdose reports that are sent as Periodic ICSRs (not serious by EU definition unless other serious criteria met, but serious for US/FDA) as they will be 'serious' in our database but all E2b serious criteria will be No. Proposed change: Reconsider rule in light of Transatlantic Simplification	Proposed change not accepted. "Cancer" criterion is not mixed with Overdose even in the US. "Cancer" is by definition "medically important" and "serious" in the EU. There is no difference between EU and US.
Appendix A – Section A.1 Business Rules applicable to	Voisin	Comments: Add the following data element B.1.2.1.a, *patientbirthdateformat*, Type = N, Values = (102), Mandatory = blank, Notes = see Note 1.	Proposed change accepted.

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the EVPM and EVCTM (Error Generation), Table 2, Page 37			
Appendix A – Section A.1 Business Rules applicable to the EVPM and EVCTM (Error Generation), Table 2, Page 40	Voisin	Comments: Add the following data element B.2.i.4.a, *reactionstartdateformat,* Type = N, Values = (102, 203, 610, 602), Mandatory = blank, Notes = see Note 1.	Proposed change accepted.
		Comments: Add the following data element B.3.1.e, *testunit*, Type = AN, Mandatory = "Mandatory if B.3.1d is not NULL", Notes = blank	Proposed change not accepted. Test unit is not always available from the primary source. If no test unit is reported, this proposal would require entering systematically NOS in order to avoid the generation of an error message.
		Comments: Add the following data element B.4.k.12.a, *drugstartdateformat,* Type = N, Values = (102, 610, 602), Mandatory = blank, Notes = see Note 1.	Proposed change accepted.
Appendix A – Section A.1 Business Rules applicable to the EVPM and EVCTM (Error Generation), Table 2, Page 40	Voisin	Comments: We recommend adding the data element B.4.k.13.1.a, *drugstartperiod*, as mandatory if B.4.k.12.b *drugstartdate* and B.2.i.4.b *reactionstartdate* are filled in.	Proposed change not accepted. Not all organisations are calculating periods and this would require dates to be of the same format to be applicable.
	Voisin	Comments: We recommend adding the data element B.4.k.13.2.a, *druglastperiod,* as mandatory if B.4.k.14.b *drugenddate* and B.2.i.4.b *reactionstartdate* are filled in.	Proposed change not accepted. Not all organisations are calculating periods and this would require dates to be of the same format to be applicable.

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Appendix A, Note 1, Page 42 and Note 4, Page 57	AGEMED	Comments: The use of non-valid alphanumeric MedDRA terms/codes generates an error message in the validation process. Proposed change: It is our understanding that only MedDRA codes should be transmitted.	Proposed change partly accepted. The use of non-valid numeric MedDRA LLT codes generates an error message in the validation process (except in the data element *testname* (ICH E2B(R2) B.3.1c) where valid MedDRA LLT names are also accepted).
Appendix A, Note 2, Page 42 and Note 8, Page 58		Comments: When the value of the data element *observestudytype* is 2 or 3, the accepted value for the data element *reporttype* is 2. Proposed change: We do not agree with this business rules since a case could be reported by different primary sources. An initial case could be spontaneously reported by a pharmacist, we will code it a *reporttype*=1. If later, the same case is notified by a GP as observational study, we will add another primary source without changing *reporttype*.	Proposed change not accepted. Chapter added in Note: When follow-up information impacts on the type of report or the type of study, the report should always be reclassified with the most specific information. For example, - When an ICSR is initially submitted with the value '1' (spontaneous report) in the data element *reporttype* (ICH E2B(R2) A.1.4), it should be reclassified with the value '2' (report from study) if this information is available in the follow-up report and the data element *observestudytype* (ICH E2B(R2)A.2.3.3) should be populated with the appropriate value. - When an ICSR is initially submitted to EVPM with the value '2' (individual patient use) or '3' (other studies) in the data element *observestudytype* (ICH E2B(R2)A.2.3.3), it should be reclassified with the value '1' (clinical trial) if this information is available in the follow-up report. The corresponding follow-up ICSR should be submitted to EVCTM. No nullification of the initial report should be done in EVPM.
Appendix A, Note 6, Page 43	BfArM	Comments: If the death of the patient is unrelated to the reported event(s)/reaction(s), only the element *patientdeath* should be completed. However this may lead to a report, where the death	Proposed change not accepted. ICH E2B guideline needs to be followed. When the death, according to both the reporter and the sender, is unrelated to the reaction/event, death should not be entered as outcome, but

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		of a patient is hidden in the narrative, if data for the section '*patientdeath*' is not available. In the current proposal the information about the death of a patient is held in a redundant manner as it is coded in one of the reaction outcome sections as well as in the seriousness section, if there is any causality between the drug(s) used and the fatal outcome of the adverse reaction/event. Proposed change: Therefore, if the patient died, the field *seriousnessdeath* should always be ticked irrespective of any causality between the drug(s) used and the death of the patient.	should be reported under section ICH E2B(R2) B.1.9 where information about the patient's death is described. The case should not be considered as fatal. The data element *Seriousnessdeath* (ICH E2B(R2) A.1.5.2) should not be flagged as yes. This is particularly important for example in some cases where disease progression unrelated to the reaction/event leads to the death of the patient.
Appendix A, Note 7, Page 43	DDCS	Comments: How to proceed for SUSARs reported in the literature if the EudraCT number or EV code are not available in the article	This will be addressed in the context of Questions and Answers and included in Volume 10.
Appendix A, Note 7, Page 43	MSD	Comments: SUSARs in EEA must have valid EudraCT number, however long term (e.g. endpoint) studies may still be ongoing that pre-date EudraCT. This must be taken into account.	Chapter added in Note 7: The following generic EudraCT Number is provided for all interventional clinical trials including a centre in a Member State and started before 01 May 2004 (or before the clinical trial Directive 2001/20/EC has been implemented in a Member State): **EVCT-000000-16**. It should be used in the data element *studyname* (ICH E2B(R2) A.2.3.1 <u>for these interventional clinical trials only</u>.

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Appendix A, Note 7, Page 43	MSD	Comments: SUSARS outside EEA must have a valid EudraCT number or DMP EV code. This will require Sponsors/MAHs to program mappings such that when EudraCT is null, DMP is populated instead. The concern here is that, until ICH M5 is finalised and implemented by all, there may be instances where DMP codes are not available for all products in non-EU study cases needing to be submitted (e.g. an ex-EU ICSR where the product is marketed but not being used in studies in EU).	See comment from EFPIA concerning Note 7b Page 43.
Appendix A, Note 7.b, Page 43	EFPIA	Comments: For SUSARs originating outside the EEA from a study involving a marketed product and not conducted in the EEA, no EUDRACT number or DMP EV code is available. The structure requested for the data element *studyname* cannot be implemented. Local clinical trial numbers for non EEA partners (e.g. FDA) are expected is the data element *studyname*, for the EMEA it is expected in the data element *sendercomment*, it is always difficult to manage different rules for same information. Proposed change: When a study has no EUDRACT number or DMP EV code, the structure of the data element *studyname* should be '#study name'	Proposed change accepted: b) For SUSARs originating outside the EEA: - 'Valid EudraCT Number#Study abbreviated name' or '#Study abbreviated name' when the values in the data elements *primarysourcecountry* (ICH E2B(R2) A.1.1) and *occurcountry* (ICH E2B(R2) A.1.2) are non-EEA countries.
Appendix A, Note 10, Page 44 and Note 15, Page 60	AGEMED	Comments: Each corresponding start date and end date should be presented with the same data format Proposed change:	Proposed changed not accepted. Information should be presented as reported.

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		We believe that the information should be captured as exact as possible. Where the original reporter states just a year start date but a complete end date, the exact date should be entered even if we do not know the exact date for the other interval.	
Appendix A, Note 12, Page 44	EFPIA	Comments: The presence of the data element *activesubstancename* (ICH E2B(R2) B4.k.2.2) is mandatory when the value in the data element *drugcharacterisation* (ICH E2B(R2) B4.k.1) is '1' (suspect) or '3' (interacting). It may occur that the only information we have concerning an interaction is the class of the drug, e.g. beta-blockers… In this case it is impossible to populate the active substance name. Proposed change: A warning should be generated instead of an error.	Proposed change partly accepted. Note 12 Appendix A: For cases submitted to EVCTM, the population of the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) is mandatory when the value in the data element *drugcharacterisation* (ICH E2B(R2) B.4.k.1) is '1' (suspect) or '3' (interacting). Failure of this validation generates an error. Note 2 Appendix B: For cases submitted to EVPM, the data element *activesubstancename* (ICH E2B(R2) B.4.k.2.2) should be populated when the value in the data element *drugcharacterisation* (ICH E2B(R2) B.4.k.1) is '1' (suspect) or '3' (interacting). Failure of this validation generates a warning.
Appendix A, Note 12, Page 44	BfArM	Comments: It is required that either the field *medicinalproduct* or *activesubstancename* has to be completed. However from our point of view this requirement is insufficient as NCAs normally do not know about the active ingredients of drugs on foreign markets. So it is essential to have the information of both items provided in a case report to make the information interpretable to the recipient. In contrast, use and provision of data to the EVMPD is not mandatory and direct reporting of sponsors to the EMEA is not mandatory in all countries and not required by Dir 2001/20 or Note for Guidance ENTR/CT3. The EVMPD is therefore not necessarily complete and in addition not available to NCAs for incorporation into their own systems if they wish to.	Proposed changed not accepted. At least one of the data elements, active substance name (ICH E2B (R2) B.4.k.2.2) or medicinal product name (ICH E2B (R2) B.4.k.2.1) needs to be populated for each medicinal product reported in the drug section (ICH E2B (R2) B.4). The revised business rules are making mandatory the population of the data element *activesubstancename* (ICH E2B (R2) B.4.k.2.2) for suspected or interacting medicinal product(s) when submitting SUSARs to the EudraVigilance Clinical Trial Module. Failure to this requirement will generate an error message and the case will need to be corrected and resubmitted by respecting the expedited reporting timeline of the original report. In addition the failure to populate the data element active substance name (ICH E2B (R2) B.4.k.2.2) for suspected or

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		Proposed change: Active substances, i. e. the respective INN-names, should always be provided in addition to medicinal product.	interacting medicinal products when submitting ICSRs to the EudraVigilance Post Authorisation Module will generate a warning message. In certain situations, it is not possible for the sender of the ICSR to provide the information in both data elements especially for concomitant medications, where the exact composition is often not known to the Sender even if attempts are made to obtain further information. Following completion of the international standardisation work on IDMP, this could be revisited.
Appendix A, Note 14, Page 44	MSD	Comments: With respect to the rules for defining Medically confirmed (for initial non-HCP reports), this would require many MAHs to make both database and procedural changes. In addition, due to the level of detail/complexity, implementation will require extensive user training. Is this level of complexity needed and if so, what period will users have to introduce such changes?	Validation rules changed to a recommendation. It will also be included in training material.
Appendix B, Note 3, Page 47	AGEMED	Comments: The failure of a successful match with the MedDRA lookup for the *testname* field generates a warning. Proposed change: We suggest that failure to match with the MedDRA codes lookup should generate an error and not a warning.	Proposed change partly accepted: Note 15 Appendix A: The ICSRs including tests should report in the data element *testname* (ICH E2B(R2) B.3.1c) a valid MedDRA LLT name or code. The failure of a successful match with the MedDRA lookup generates an error. If necessary, test names and results can be provided in free text in the data element *resultstestsprocedures* (ICH E2B(R2) B.3.2).
Appendix B: Business Rules (Warning Generation), Page 46	Voisin	Comments: This chapter reflects the list of the business rules (Table 5), generating warnings by EV7.1. Proposed change: We suggest you add the following:	Proposed change accepted.

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		This chapter reflects the list of the business rules applicable to the EVPM and EVCTM (Table 5), generating warnings by EV7.1.	
Appendix B: Business Rules (Warning Generation), Page 46, Table 5	Voisin	Comments: We suggest that you remove the data element B.3.1.e, *testunit*, from the Business Rules generating a warning message and include it in the Business Rules generating an error message. See previous comment.	Proposed changed not accepted. Test unit is not always available from the primary source. If no test unit is reported, this proposal would require entering systematically NOS to avoid the generation of an error message.
Appendix B, Note 4, Page 47	EFPIA	Comments: If there is no match with the Pharmacopoeia, the form must be only in the narrative. Non-EEA countries/partners will not understand why the form is not populated in B.4.k.7 if the information is in the narrative.	Proposed changed not accepted. The system generates warning massages if the information entered does not match with the Pharmacopeia. Non-EEA stakeholders have the possibility to enter information with non matching terms in the data element B.4.k.7.
Appendix C-Section C.1 Business Rules applicable to the EVPM and EVCTM (Error Generation) Table 6, Page 48	Voisin	Comments: In the data element M.1.6, *messagereceiveridentifier*, the "Values" column should be completed with the following: "- 'EVTEST' = Test environment – EVPM - 'EVHUMAN'= Production environment – EVPM - 'EVCTMTEST' = Test environment – EVCTM - 'EVCTMPROD' = Production environment – EVCTM"	Proposed change partly accepted: Note added: When submitting a Safety Message to EV, the value accepted in the data element *messagereceiveridentifier* (ICH M2 M.1.5) is one of the following, depending to which module the message is addressed: - 'EVTEST' (Test environment – EVPM) - 'EVHUMAN' (Production environment – EVPM) - 'EVCTMTEST' (Test environment – EVCTM) - 'EVCTMPROD' (Production environment – EVCTM).
Appendix C-Section C.1 Business	Voisin	Comments: In the data element A.1.10.1, *authoritynumb*, the "Notes" field should be completed with "NULL if A.1.10.2".	Proposed change partly accepted: One of A.1.10.1 or A.1.10.2 accepted.

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Rules applicable to the EVPM and EVCTM (Error Generation) Table 6, Page 48		Comments: In the data element A.1.10.2, *companynumb*, the "Notes" field should be filled in with "NULL if A.1.10.1".	Proposed change partly accepted: One of A.1.10.1 or A.1.10.2 accepted.
Appendix C-Section C.1 Business Rules applicable to the EVPM and EVCTM (Error Generation) Table 6, Page 49	Voisin	Comments: Based on practice, it is usually difficult to include the entire protocol title in the study name field (ICH E2B(R2) A.2.3.1). Therefore, we suggest you to increase the number of limited characters above 100 or to provide a naming convention for the study name as example of guide.	Sentence added: If necessary the study name should be abbreviated in the data element *studyname* (ICH E2B(R2) A.2.3.1). The entire study name can eventually be included in the data element *narrativeincludeclinical* (ICH E2B(R2) B.5.1).
Appendix C Section C.1 Business Rules applicable to the EVPM and EVCTM (Error Generation) Table 6, Page 50	Voisin	Comments: Add the following data element B.1.2.1.a, *patientbirthdateformat*, Type = N, Values = (102), Mandatory = blank, Notes = blank.	Mandatory field updated: Mandatory if B.1.2.1b is not NULL

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Appendix C-Section C.1 Business Rules applicable to the EVPM and EVCTM (Error Generation) Table 6, Page 51	Voisin	Comments: We suggest that in the data element B.1.7, *medicalhistoryepisode*, the "Notes" field should be completed with "(1… . ∞)".	Proposed change accepted.
		Comments: We suggest that in the data element B.1.8, p*atientpastdrugtherapy*, the "Notes" field should be completed with "(1… .∞)".	Proposed change accepted.
Appendix C-Section C.1 Business Rules applicable to the EVPM and EVCTM (Error Generation) Table 6, Page 52	Voisin	Comments: We suggest that in the data element B.1.9.2.b, *patientdeathreport,* the "Notes" field should be completed with "(1… . ∞)".	Proposed change partly accepted. Line B.1.9.2 added with (1...∞) in Notes.
		Comments: We suggest that in the data element B.1.9.4.b, *patientautopsy*, the "Notes" field should be completed with "(1… . ∞)".	Proposed change partly accepted. Line B.1.9.4 added with (1...∞) in Notes.
		Comments: We suggest that in the data element B.1.10.7, *parentmedicalhistoryepisode,* the "Notes" field should be completed with "(1… . ∞)".	Proposed change accepted.
Appendix C-Section C.1 Business Rules applicable to the EVPM and EVCTM	Voisin	Comments: We suggest that in the data element B.1.10.8, *parentpastdrugtherapy*, the "Notes" field should be completed with "(1… . ∞)".	Proposed change accepted.

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(Error Generation) Table 6, Page 53			
Appendix C-Section C.1 Business Rules applicable to the EVPM and EVCTM (Error Generation) Table 6, Page 54	Voisin	Comments: We suggest you make the field B.3.1.e unit for lab results a mandatory field generating an error message, since lab results with no unit are irrelevant. In order to be able to enter non-numerical assessment of lab tests, we suggest you to create an additional field for comments. For this additional field the unit completion should not be mandatory.	Proposed changed not accepted. Test unit is not always available from the primary source. If no test unit is reported, this proposal would require entering systematically NOS to avoid the generation of an error message.
Appendix C-Section C.1 Business Rules applicable to the EVPM and EVCTM (Error Generation) Table 6, Page 55	Voisin	Comments: We suggest that in the data element B.4.k.17.2b, *drugrecurrence,* the "Notes" field should be completed with "(1… . ∞)".	Proposed change partly accepted. Line B. 4.k.17.2 added with (1...∞) in Notes.
		Comments: We suggest that in the data element B.4.k.18, *drugreactionassess*, the "Notes" field should be completed with "(1… . ∞)". Regarding the expedited reporting criteria, the drug relatedness is mandatory. We think that this *drugrelatedness* should be a mandatory data element, and therefore, generating warning/error message if not filled.	Proposed change partly accepted. "(1… . ∞)" added in Notes. Mandatory Drug relatedness not accepted as there is currently no internationally standardised way to report drug relatedness.
Appendix C Note 10 (medically confirm) Pages 58-59	EFPIA	Comments: The document states that if the primary source is a health professional 'the data element medically confirm A.1.14 should not be populated'	Validation rules changed to a recommendation. It will also be included in training material.

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		This presents a potential issue for a company whose current safety database – Argus 4.1 – because this field is in the form of a radio button. Their current data entry practice is to populate that field in all case reports. Once selected (even in error) it is not possible to unselect this filed which means that such a case would generate an error message. The other point regarding the same data element concerns searching. If this data element is not populated, searching for GCP confirmed cases becomes more complicated. The companies would have to search for all the possible variations on qualification, e.g. physician, pharmacist or other HCP.	
Figure 9, Page 64	DDCS	Comments: Replace 'Product Report' by 'Product Report Database', 'Scientific Product' by 'Scientific Product Database', 'Product Index' by 'Product Index Database'.	Proposed change accepted.
Scientific Product Database chapter, Page 65	DDCS	Comments: Remove 'dose' in 'Pharmaceutical dose form'.	Proposed change accepted.
Section D.4.1, Page 66	Wyeth	Comments: It is unclear if a variation of the Full Presentation Name (e.g. name not exactly matching with the SPC) will be accepted using the new validation rules. Proposed change: If a MAH has previously submitted product data to the EudraVigilance Medicinal Product Dictionary and a variation of the Full Presentation Name was provided, the EMEA should accept the product data in an incoming ICSR using this	Proposed changed not accepted. A variation of the full presentation name by the MAH needs to be updated by the MAH in the EVMPD.

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		variation.	
Example of splitting, Page 66	DDCS	Comments: Remove XYZ for Product Strength and Product Pharmaceutical Form. Include reference to guideline for vaccines.	Proposed change accepted. Guideline for vaccines entry in EVMPD is available in EV Q&As.
Chapter D.5.2, Page 69	DDCS	Comments: Replace Product Database by Product Report Database.	Proposed change accepted.
Pharmaceuticalformcode, Page 78	DDCS	Comments: Replace by The filed contains the EudraVigilance code of the corresponding pharmaceutical form term.	Column renamed by Dosageformcode: The EV code of the corresponding dosage form term.
Appendix 1, Term in relation to electronic exchange of safety information, Page 83	Voisin	Comments: We suggest adding the following definition: "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 semiautomatic way using the EudraVigilance web application, EVWEB."	Proposed change accepted.
	DDCS	Comments: Present definition of Acknowledgement of Receipt is a definition of validation and not acknowledgement.	Definition corrected to: An acknowledgment of receipt is a message created and returned to the sender organisation, recognising that a message has been received.