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

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EUDRAVIGILANCE EXPERT WORKING GROUP

VOLUME 9A IMPLEMENTATION QUESTIONS & ANSWERS

Version 3.2

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EXECUTIVE SUMMARY

The EudraVigilance Expert Working Group and the EudraVigilance Steering Committee, in consultation with the CHMP Pharmacovigilance Working Party, have developed a series of Questions and Answers (Q&As) to address frequently asked implementation questions from stakeholders in relation to Volume 9A of the Rules Governing Medicinal Products in the European Union: Pharmacovigilance for Medicinal Products for Human Use. Version 1.2 was released in February 2008. Two new sets of Q&As (version 2.1 and 3.2) were added in October 2008.

Document History

Q&As Versions	Questions Reference Numbers	Date	Description
1.2	001 to 018	September 2007 October 2007 December 2007	EudraVigilance Expert Working Group
		November 2007 December 2007	CHMP Pharmacovigilance Working Party
		February 2008	EudraVigilance Steering Committee
2.1	019 to 030	March 2008 April 2008	EudraVigilance Expert Working Group
		April 2008 May 2008	CHMP Pharmacovigilance Working Party
		October 2008	EudraVigilance Steering Committee
3.2	031 to 037	June 2008 July 2008 September 2008	EudraVigilance Expert Working Group
		September 2008	CHMP Pharmacovigilance Working Party
		October 2008	EudraVigilance Steering Committee

BACKGROUND

This Q&A document provides conventions for the harmonised interpretation of Volume 9A of the Rules Governing Medicinal Products in the European Union: Pharmacovigilance for Medicinal Products for Human Use. Stakeholders e.g. marketing authorisation holders (MAHs), National Competent Authorities (NCAs), vendors, contract research organisations can submit implementation-related questions to the EudraVigilance Expert Working Group (EV-EWG). Questions can be submitted to eudravigilance@emea.europa.eu.
Answers to these questions are developed by the EV-EWG in consultation with the CHMP PhVWP based on a consensus process.

Questions requiring immediate answers in relation to national requirements should be addressed directly to the appropriate NCAs.

Where reference is made to the ICH E2B(R2) guideline, please note that this was previously referred to as ICH E2B(M) guideline: Maintenance of the Clinical Safety Data Management including Data Elements for Transmission of Individual Case Safety Reports. The tripartite harmonised ICH guideline was finalised as E2B (Step 4) in July 1997 and amended for Maintenance as E2B(R1) on 10 November 2000. Post Step 4 editorial corrections were given on 5 February 2001 (second revision) and the guideline renamed E2B(R2).

Questions and Answers related to Volume 9A			
Date of Approval	**Reference Number**	**Question**	**Answer**
Dec-2007	ID: 001	A literature article describes serious adverse reactions that have been experienced by a large number of patients. How should ICSRs be cross-referenced to the same article?	If a literature article describes up to three patients as referred to in Table 'III.7.A: Example for the reporting of cases originally reported in the worldwide literature referring to more than one patient' of Volume 9A, three ICSRs should be submitted, reporting for each individual patient the adverse reaction(s) and all other available information on the case. In addition, all ICSRs which relate to the same literature article should be cross referenced in the section ICH E2B(R2) field A.1.12 'Identification number of the report which is linked to this report' and the section should be repeated as necessary to cross refer all the three related cases. However, if a literature article describes more than three patients, for each patient an ICSR should be submitted, reporting for each individual patient the adverse reaction(s) and all other available information on the case. For the ICSRs which relate to the same literature article, the cross reference in the section ICH E2B(R2) field A.1.12 *'Identification number of the report which is linked to this report'* should be conducted as follows: ▪ The first case should be linked to all other cases related to the same article ▪ All the other cases should be only linked to the first one, as in the example below *Example for the reporting of cases originally reported in the worldwide literature referring to a large number of patients* For Case 1 described in the literature article: - ICH E2B(R2) A.1.10.1 *'Worldwide Unique Case Identification Number'*: UK-ORGABC-0001 - ICH E2B(R2) A.1.12 *'Linked Report'*: UK-ORGABC-0002 - ICH E2B(R2) A.1.12 *'Linked Report'*: UK-ORGABC-0003 - ICH E2B(R2) A.1.12 *'Linked Report'*: UK-ORGABC-0004 - ICH E2B(R2) A.1.12 *'Linked Report'*: UK-ORGABC-000N - ICH E2B(R2) A.2.2 *'Literature reference(s)'*: N Engl J Med. 1997;336:309-15. - File name for the copy of literature article to be sent via e-mail to EVLIT@emea.europa.eu: UK-ORGABC-0001.pdf

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			For Case 2 described in the literature article: - ICH E2B(R2) A.1.10.1 *'Worldwide Unique Case Identification Number'*: UK-ORGABC-0002 - ICH E2B(R2) A.1.12 *'Linked Report'*: UK-ORGABC-0001 - ICH E2B(R2) A.2.2 *'Literature reference(s)'*: N Engl J Med. 1997;336:309-15. No copy of the literature article required since the copy was already submitted for case 1. For Case N described in the literature article: - ICH E2B(R2) A.1.10.1 *'Worldwide Unique Case Identification Number'*: UK-ORGABC-000N - ICH E2B(R2) A.1.12 *'Linked Report'*: UK-ORGABC-0001 - ICH E2B(R2) A.2.2 *'Literature reference(s)'*: N Engl J Med. 1997;336:309-15. No copy of the literature article required since the copy was already submitted for case 1.
Dec-2007	ID: 002	Do the Data Privacy rules for 'Patient name or initials' in paper or E2B format applies to submissions to EudraVigilance and NCAs?	The guidance provided in Volume 9A chapter III.5, Section 4 'What to Take into Account for Data Privacy Laws' regarding patient name or initials reads as follows: 'To comply with EU legislation on the protection of individuals with regard to the processing of personal data as referred to in Chapter I.7, Section 7, electronic transmission of ICSRs should operate on the principles of anonymised information, whereby the ICH guidelines should be adhered to as follows: ▪ ICH E2B(R2) field B.1.1 '*Patient name or initials*': The information should be provided when it is in conformance with the confidentiality requirements. This also applies to medical record number(s) ICH E2B (R2) field (B.1.1.1). If the initials are known to the sender but cannot be transmitted due to data privacy requirements, this field should be populated with 'PRIVACY'. If the initials of the patient are unknown to the sender, this field should be populated with 'UNKNOWN'. The same principles apply for ICH E2B(R2) section A.2 *'Primary source(s) of information'* and section B.1.10 *'For a parent-child/fetus report, information concerning the parent'*. The guidance provided in Volume 9A is applicable to: ▪ Submissions to EudraVigilance to both EVHUMAN and EVCTMPROD

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			▪ Submissions to all NCAs in the EEA depending on each NCA's own implementation of the data protection requirements as per national legislation In practice in some EEA countries stakeholders may be asked/permitted to provide patient's initials but in others, where the provision of initials or patient names is not permitted according to national legislation, the provisions as outlined above should be followed (i.e. populate the field with 'PRIVACY'). In this context the data privacy rules interfere with the concept of the 'identifiable patient' because depending on the level of detail of information available on the case, you may be able to identify the patient. That is the reason why some NCAs accept to receive the patient's initials but require deleting them from the forms or the electronic submissions of ICSRs when the cases should be reported outside the country of origin. In order to avoid a high degree of customisation for reporting to each NCA, the rule described in the Volume 9A may therefore be applied in every circumstance.
Dec-2007	ID: 003	How should the fields ICH E2B(R2) B.4.k.2.1 *'Proprietary medicinal product name'* and ICH E2B(R2) B.4.k.2.2 *'Active substance name(s)'* in the ICSR be populated, where the active ingredients of a branded medicinal product could be one of two possible generics, depending on the country in which it is marketed?	Where the primary source reported a suspect or interacting branded/proprietary medicinal product name without indicating the active substances of the medicinal product and the proprietary medicinal product could be one of two or more possible generics, which have a different composition depending on the country where the medicinal product is marketed, the ICSR should be populated as follows: ▪ Field ICH E2B(R2) B.4.k.2.1 *'Proprietary medicinal product name'* should be populated with the proprietary/branded medicinal product name as reported by the primary source. ▪ Field ICH E2B(R2) B.4.k.2.2 *'Active substance name(s)'* should be completed with those active substances that correspond to the composition of the proprietary/branded medicinal product of the country where the reaction/event occurred (field ICH E2B(R2) A.1.2) or if this is the same, of the country of the primary source, (field ICH E2B(R2) A.1.1). In cases, where information is available on: ▪ The *'Identification of the country where the drug was obtained'* (field ICH E2B(R2) B.4.k.2.3), ▪ The *'Authorization/application number'* (field ICH E2B(R2) B.4.k.4.1), ▪ The *'Country of authorization/application'* (field ICH E2B(R2) B.4.k.4.2) and/or ▪ The *'Batch/lot number'* (field ICH E2B(R2) B.4.k.3) The composition with regard to the active substances of the proprietary medicinal product should be provided

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			accordingly. In any cases, the field ICH E2B(R2) B.4.k.2.2 *'Active substance name(s)'* field needs to be repeated for each active substance.
Dec-2007	ID: 004	How should the fields ICH E2B(R2) B.4.k.2.1 *'Proprietary medicinal product name'* and ICH E2B(R2) B.4.k.2.2 *'Active substance name(s)'* in the ICSR be populated, where the active ingredients of a branded medicinal product differ depending on the formulation/presentation marketed?	In case the primary source reports a suspect or interacting branded/proprietary medicinal product name without indicating the formulation/presentation of the product and the proprietary/branded medicinal product can be one of two or more possible formulations/presentations in a country, which have a different composition, the ICSR should be populated as follows: ▪ Field ICH E2B(R2) B.4.k.2.1 *'Proprietary medicinal product name'* should be populated with the medicinal product name as reported by the primary source. ▪ Field ICH E2B(R2) B.4.k.2.2 *'Active substance name(s)'* should be completed with those active substances that correspond to the formulation/presentation of the proprietary medicinal product which are in common to all formulations/presentations in the country of authorisation. In situations, where the active substances of a proprietary medicinal product could be one of two possible generics, depending on the country in which it is marketed, the guidance should be followed as provided for question ID: 0003. The ICH E2B(R2) B.4.k.2.2 *'Active substance name(s)'* field needs to be repeated for each active substance.
Dec-2007	ID: 005	How should the fields ICH E2B(R2) B.4.k.2.1 *'Proprietary medicinal product name'* and ICH E2B(R2) B.4.k.2.2 *'Active substance name(s)'* in the ICSR be populated, where the co-medication was reported as e.g. a class of	Drug information, which is reported as concomitant or interacting medication and which cannot be characterized by the proprietary medicinal product name or by the active substances (e.g. antineoplastic agents), should not be captured in B.4.k.2.1 *'Proprietary medicinal product name'* and ICH E2B(R2) B.4.k.2.2 *'Active substance name(s)'*. Instead this information should be provided in field B.5.1 *'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information'*. The same applies e.g. if a food interaction is reported (e.g. grapefruit juice). As regards the reporting of drug interactions, which includes drug/drug (including biological products), drug/food, drug/device, and drug/alcohol interactions, the coding should be performed in section B.2 *'Reactions/Events'* in line with the latest version of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to

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		medicinal products?	Consider'.
Dec-2007	ID: 006	Is it acceptable for MAHs to report all serious adverse drug reactions occurring outside the European Union to all NCAs?	In line with Volume 9A of 'The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use', Chapter III.11 Section 3 'Reporting of all Serious Cases from outside the European Union', MAHs are encouraged to report electronically to EudraVigilance all suspected serious adverse reactions that occur in a third country for all medicinal products authorised in the EU, regardless of the authorisation procedure (national, centralised, decentralised or mutual recognition procedures). As regards the reporting to NCAs, MAHs should follow the requirements as set out in Volume 9A Annex 6.1.3 'Specific Expedited (15-days) Reporting Requirements in Member States for ICSRs from Spontaneous Reporting and Non-Interventional Studies Occurring Outside the EU'.
Dec-2007	ID: 007	Will it be possible to send copy of literature articles via the EudraVigilance Gateway?	Until the revised ICH standards are available, copies of literature articles should be submitted in line with the requirements provided in Volume 9A of 'The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use', Chapter III.7 'Handling of Adverse Reaction Reports Published in the Worldwide Literature'. In the frame of the revision of the ICH E2B(R2) guideline, the requirement to be able to submit electronic copies of literature articles and associate those with the ICSRs concerned have been put forward by the EU and EFPIA.
Dec-2007	ID: 008	Some NCAs request MAHs to nullify a case because they received a report for that patient from a second MAH. How should nullifications be managed?	In Volume 9A, part II 'Guidelines for Competent Authorities and the Agency', chapter II.1 Section 3.3 'Processing Individual Case Safety Reports' the management of duplicates by NCAs is described. It is stated that the NCA should make every effort to ensure that case reports contain sufficient information to identify such duplicates and should liaise with relevant MAHs to facilitate identification of possible duplicate cases. Databases should be reviewed regularly to identify duplicates in accordance with the NCA and Agency procedures. Where e.g. two MAHs may have submitted a report for the same case, after identification, the NCA should merge the duplicates into a single new (or merged) ICSR in accordance with ICH E2B (R2) guidance (see Volume 9A, Chapter III.6 'Nullification of Individual Cases'). Note that in this scenario a nullification of the case is not

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			applicable.
Dec-2007	ID: 009	How should the retrospective transmission of ICSRs to EudraVigilance be conducted when it may not be possible to differentiate between interventional and non-interventional clinical trials going back to 1995?	The retrospective transmission of ICSRs to EudraVigilance (Post-Authorisation Module) should be conducted in line with the provisions set out in Volume 9A, part Chapter III.11 Section 4'Retrospective Electronic Population of EudraVigilance Post-Authorisation Module'. Where it is not possible for the MAH to differentiate between interventional and non-interventional clinical trials, all cases should be submitted to the EudraVigilance Post-Authorisation Module (EVPM) back to 1 May 2004. According to Directive 2001/20/EC, as of 1st May 2004 all reports arising from interventional clinical trials need to be submitted to the EudraVigilance Clinical Trial Module (EVCTM) and should therefore not be retrospectively submitted to EVPM. As a general principle the Agency should be informed when the retrospective transmission of ICSRs is initiated and what data set will be provided. Furthermore, the Agency should be informed once the retrospective transmission of ICSRs to the EudraVigilance Post-Authorisation Module has been completed successfully.
Dec-2007	ID: 010	How should a MAH handle a case when there is partial confirmation of a consumer case by a health care professional (HCP) .i.e. a consumer reported 5 events but the HCP only confirms 2 of those reported?	Cases initially reported e.g. by a consumer or a lawyer, where at least one adverse event has been medically confirmed should be reported as medically confirmed. The field A.1.14 *'Was report medically confirmed if not initially from health care professional'* should be set to 'Yes'. In the field ICH E2B(R2) B.5.1 *'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information'* any relevant information on the medical confirmation of the case should be also included.
Dec-2007	ID:011	In spontaneous reports the primary source often provides the diagnoses as well as signs and symptoms related to adverse reactions in the	The coding of diagnoses and provisional diagnoses with signs and symptoms in the ICH E2B(R2) field B.2.i.1 *'Reaction/event in MedDRA terminology (Lowest Level Term)'* should be performed in line with the latest version of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider'. In practice, events, which are typically signs or a symptoms of a diagnosis or a provisional diagnosis reported by a primary source/reporter, should be listed and MedDRA coded in the ICH E2B(R2) section B.2

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		narrative section of the reporting forms. Should the diagnoses as well as the signs and symptoms be listed in the ICH E2B(R2) section B.2 *'Reaction(s)/event(s)'* when an ICSR is prepared?	*'Reaction(s)/event(s)'* but it is considered sufficient to select a term for only the diagnosis or provisional diagnosis and not for the sign and symptoms. If in the narrative other events have been reported by the primary source, which are not typically signs or symptoms of the primary source's/reporter's diagnosis or provisional diagnosis, and those events are suspected to be adverse reactions, then they should be listed and MedDRA coded in the ICH E2B(R2) section B.2 *'Reaction(s)/event(s)'*. If no diagnosis is provided by the primary source, all reported signs and symptoms should be listed and MedDRA coded in the ICH E2B(R2) section B.2 *'Reaction(s)/event(s)'*. In addition, if signs and symptoms are typically part of a diagnosis then the diagnosis can be MedDRA coded in the field ICH E2B(R2) B.5.3 *'Sender's diagnosis/syndrome and/or reclassification of the reaction/event'*.
Dec-2007	ID:012	How should the requirements of Volume 9A regarding the literature reporting and marketing authorisation of medicinal products be interpreted. The question refers to scenario, where the medicinal product source and/or the invented name is not specified and ownership of the product cannot be excluded on the basis of the active substance(s), formulation or route of administration and the MAH. In	In Volume 9A, Chapter I.4 Section 3.2 'Reports published in the worldwide literature' it is stated: 'if the medicinal product source and /or the invented name is not specified and ownership of the product cannot be excluded on the basis of the active substance, formulation or route of administration, the MAH should assume that it is one of their products the publication refers to, although the report should indicate that the specific product source and the invented name was not identified.' As regards the interpretation of the 'medicinal product source' the MAH may also take the occurrence or the primary source country of the adverse reaction(s) into account to assume that it is one of their products. In practice this means that if in reports published in the world literature the occurrence or the primary source country is provided and the MAH does not have a marketing authorisation in this country, the company does not need to submit these cases. The likelihood to miss reports published in the worldwide literature is negligible compared to the number of potential duplicates submitted for the same case by various companies.

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		particular, clarification is needed, if the country where the case occurred can be used to exclude the ownership of the product?	
Dec-2007	ID: 013	As pointed out in Volume 9A, Chapter I. 5 Section 9 'Reporting of Suspected Transmission of Infectious Agents' the requirement to apply MedDRA coding is also relevant to the reporting of cases of suspected transmission of an infectious agent. How should a suspected transmission of an infectious agent via a medicinal product be coded in MedDRA?	The coding of a suspected transmission of an infectious agent via a medicinal product in the ICH E2B(R2) ICSR field B.2.i.1 *'Reaction/event in MedDRA terminology (Lowest Level Term)'* should be performed in line with the latest version of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider'. In accordance with this guide, the following principles apply: If a report of transmission of infectious agent via medicinal product is received, it is considered appropriate to select a term for the transmission i.e. one of the following terms: ▪ **'*Suspected transmission of an infectious agent via a medicinal* product':** choose this term, if there is a suspicion that a transmission via a medicinal product has taken place in the patient. ▪ **'*Transmission of an infectious agent via a medicinal product*':** choose this term, if there is evidence that the infectious agent has been transmitted via a medicinal product. In addition, if the infectious agent is specified, it is considered appropriate to select the specific infectious agent as a second term. For example: If 'suspected transmission of Hepatitis C via a blood product' is reported, 'Suspected transmission of an infectious agent via a medicinal product' and 'Hepatitis C' should be selected. For electronic reporting such cases should to be classified as serious in the ICH E2B(R2) field A.1.5.1 *'Serious'*, and the ICH E2B(R2) field A.1.5.2. *'Seriousness criteria'* should be set to 'Other medically important condition' (see Volume 9 A, ICH E2B(R2) in Annex 4).

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Dec-2007	ID: 014	How should laboratory data be structured in the ICH E2B(R2) B.3 section *'Results of tests and procedures relevant to the investigation of the patient'* of the ICSR?	The coding of investigations should be performed in line with the latest version of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider'. As described in ICH E2B(R2), the section B.3 *'Results of tests and procedures relevant to the investigation of the patient'* should capture the tests and procedures performed to diagnose or confirm the reaction/event, including those tests done to investigate (exclude) a non-drug cause, (e.g., serologic tests for infectious hepatitis in suspected drug-induced hepatitis). Both positive and negative results should be reported. While structured information is preferable, provisions have been made to transmit the information as free text in the field ICH E2B(R2) B.3.2. *'Results of tests and procedures relevant to the investigation'*. **For example 'Blood glucose increased' should be coded as follows:** The 'Test name' should be provided excluding any reference to the result of the test: ICH E2B(R2) B.3.1c *'Test name'*: *Blood glucose* The 'Test result' should be coded separately: ICH E2B(R2) B.3.1d *'Test result'*: *Increased* The coding should not be as follows: ICH E2B(R2) B.3.1c *'Test name'*: *Blood glucose increased* ICH E2B(R2) B.3.1d *'Test result'*: *blank* **For example 'blood glucose 100 mg/l' or 'Blood glucose found to be normal 100 mg/l' should be coded as follows:** ICH E2B(R2) B.3.1c *'Test name'*: *Blood glucose* ICH E2B(R2) B.3.1d *'Test result'*: *100* ICH E2B(R2) B.3.1e *'Test unit'*: *mg/L* ICH E2B(R2) B.3.2 *'Results of tests and procedures relevant to the investigation'*: *Blood glucose found to be normal 100 mg/l*

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Dec-2007	ID: 015	What needs to be taken into account in populating the EVMPD as regards vaccines? Which EVMPD field should be populated?	In addition to the information on the EudraVigilance Medicinal Product Dictionary (EVMPD) population, as described in the 'EVMPD training material', specific topics related to vaccines only should be taken into account as follows: **a.** In accordance with section 1 'Name of the medicinal product' of the Summary of Product Characteristics (SmPC) or the Clinical Trial Application Form: - The medicinal product name should be entered in the EVMPD field 'Full Presentation Name' - The common name should be entered in the EVMPD field 'Generic Name' i. The 'common name' has been defined in the 'Guideline on pharmaceutical aspects of the product information for human vaccines' (Doc. Ref. EMEA/CPMP/BWP/2758/02). ii. The common name refers to the title of the relevant European Pharmacopoeia monograph, where one exists. In case where there is no European Pharmacopoeia monograph, the stylistics and precedents of European Pharmacopoeia monographs should be observed, including the use of words such as 'live', 'adsorbed' or 'virosome', in parenthesis if relevant. iii. The EVMPD contains a look-up of common names as described in the European Pharmacopoeia, which is systematically updated by the EMEA. iv. If a common name cannot be found in the EVMPD look-up, the MAH/sponsor of clinical trials should contact the EudraVigilance Helpdesk to obtain guidance on how the common name should be presented. **b.** In accordance with section 2 'Qualitative and quantitative composition' of the Summary of Product Characteristics (SmPC) or the Clinical Trial Application Form: - The vaccine antigen should be entered in the EVMPD field 'Drug Ingredient' i. The EVMPD field 'Role of Ingredient' should be set to 'Active Ingredient' ii. For each vaccine antigen a separate substance name field should be populated iii. The EVMPD contains a look-up of vaccine antigens, as described in European Pharmacopoeia or authorised in EU SmPCs which is systematically updated by the EMEA. iv. If a vaccine antigen cannot be found in the EVMPD look-up, the MAH/sponsor of clinical trials should contact the EudraVigilance Helpdesk to obtain guidance on how the antigen should be

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			presented - The vaccines adjuvant(s)/adsorbant should be entered in the EVMPD field 'Drug Ingredient' i. The EVMPD field 'Role of Ingredient' should be set to 'Excipient' ii. The strength/concentration of the vaccine adjuvant(s)/adsorbant is not required iii. For each vaccine adjuvant(s)/adsorbant a separate substance name field should be populated - The vaccine production system should not be entered in the EVMPD, as the dictionary does not currently allow for the association between the individual antigens and their adjuvants/adsorbants or the production system **c.** In accordance with section 6.1 'Excipients' of the Summary of Product Characteristics (SmPC) or the Clinical Trial Application Form: - Additional vaccine constituents should be entered in the EVMPD field 'Drug Ingredient' i. The EVMPD field 'Role of Ingredient' should be set to 'Excipient' ii. The strength/concentration of the additional vaccine constituent is not required iii. For each additional vaccine constituent a separate field should be populated Example: SmPC HBVAXPRO SmPC Section 1: 'NAME OF THE MEDICINAL PRODUCT' HBVAXPRO 5 micrograms/0.5 ml Suspension for injection Hepatitis B vaccine (rDNA) SmPC Section 2: 'QUALITATIVE AND QUANTITATIVE COMPOSITION' One dose (0.5 ml) contains: Hepatitis B virus surface antigen, recombinant (HBsAg)* 5.00 micrograms Adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.25 milligram Al+) * produced from recombinant strain of the yeast Saccharomyces cerevisiae (strain 2150-2-3) For a full list of excipients, see section 6.1

<table>
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<tr><td></td><td></td><td></td><td>SmPC Section 6.1: ‘LIST OF EXCIPIENTS’
Sodium chloride
Borax
Water for injections

Example: EVMPD entry for HBVAXPRO

Full Presentation Name HBVAXPRO 5 MICROGRAMS/0.5 ML, SUSPENSION FOR INJECTION
Product Short Name HBVAXPRO
Product Generic Name Hepatitis B vaccine (rDNA)
Product Company Name
Product Strength Name 5 MICROGRAMS/0.5 ML
Product Form Name SUSPENSION FOR INJECTION
Package Description 1 VIAL

PRD25741 - HBVAXPRO 5 MICROGRAMS/0.5 ML, SUSPENSION FOR INJECTION
MAH - AVENTIS PASTEUR MSD, SNC
Pharmaceutical Products (1)
SUSPENSION FOR INJECTION
Drug Routes (1)
Drug Ingredients (5)
HEPATITIS B SURFACE ANTIGEN (RDNA) - Active Ingredient
ALUMINIUM HYDROXYPHOSPHATE SULFATE - Excipient
WATER FOR INJECTION - Excipient
BORAX - Excipient
SODIUM CHLORIDE - Excipient</td></tr>
<tr><td>Dec-2007</td><td>ID: 016</td><td>What needs to be taken into account in populating the EVMPD as regards</td><td>In addition to the information on the EudraVigilance Medicinal Product Dictionary (EVMPD) population, as described in the ‘EVMPD training material’, the following should be taken into account:</td></tr>
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		insulins? Which EVMPD field should be populated?	**a.** In accordance with section 1 'Name of the medicinal product' of the Summary of Product Characteristics (SmPC) or the Clinical Trial Application Form: - The medicinal product name should be entered in the EVMPD field 'Full Presentation Name' **b.** In accordance with section 2 'Qualitative and quantitative composition' of the Summary of Product Characteristics (SmPC) or the Clinical Trial Application Form: - The active ingredient should be entered in the EVMPD field 'Drug Ingredient' i. The EVMPD field 'Role of Ingredient' should be set to 'Active Ingredient' ii. For each active ingredient a separate substance name field should be populated iii. The substance name should be described based on the INN iv. Where no INN is assigned to the insulin, the substance name should be populated with the terms as presented in the EVMPD look-up, which is systematically updated by the EMEA in collaboration with the CHMP BWP. v. If the appropriate insulin cannot be found in the EVMPD look-up, the MAH/sponsor of clinical trials should contact the EudraVigilance Helpdesk to obtain guidance on how the substance name should be presented. • The active ingredient can refer to an 'Insulin Substance(s)', an 'Insulin formulation(s)' or a combination of both **c.** In accordance with section 6.1 'Excipients' of the Summary of Product Characteristics (SmPC) or the Clinical Trial Application Form: - Excipients should be entered in the EVMPD field 'Drug Ingredient' i. The EVMPD field 'Role of Ingredient' should be set to 'Excipient' ii. The strength/concentration of the excipient is not required iii. For each excipient a separate substance name field should be populated As regards the characterisation of insulins the following should be taken into account: ▪ 'Insulin Substance' referring to basic insulins, which are not combined with any other particle or molecule. Insulin Substances can be described by the following elements: - Insulin Type: provides information on the final amino acid sequence (i.e. bovine, porcine or human sequence).

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			- Insulin Analogue: provides information whether the insulin has been modified in its amino acid sequence through recombinant technologies. - Insulin Class: provides information on the preparation process (e.g. Recombinant, Semi-synthetic, Non-synthetic). Example: Insulin Human rDNA Insulin Formulation: ▪ 'Insulin Formulation' referring to insulins that have been combined with other molecules or insulins. Insulin Formulations can be described by the following elements: - Physical State: provides information on the physical state of the insulin formulation following completion of the preparation process. - Complexing: provides information on the particles or molecules that have been combined with the insulin (e.g. Insulin Zinc Crystalline). - Onset of action: provides information on the onset of action of the insulin formulation referring to the time interval before the insulin reaches the bloodstream and initiates the lowering of the blood glucose (e.g. Insulin fast acting). - Duration of action: provides information on how long the insulin is lowering the blood glucose. - Example: Insulin Isophane Example 1: SmPC ACTRAPID (Insulin Medicinal Product containing an Insulin Substance) SmPC Section 1: 'NAME OF THE MEDICINAL PRODUCT' Actrapid 40 IU/ml Solution for injection in a vial SmPC Section 2: 'QUALITATIVE AND QUANTITATIVE COMPOSITION' Insulin human, rDNA (produced by recombinant DNA technology in Saccharomyces cerevisiae). 1 ml contains 40 IU of insulin human (…)

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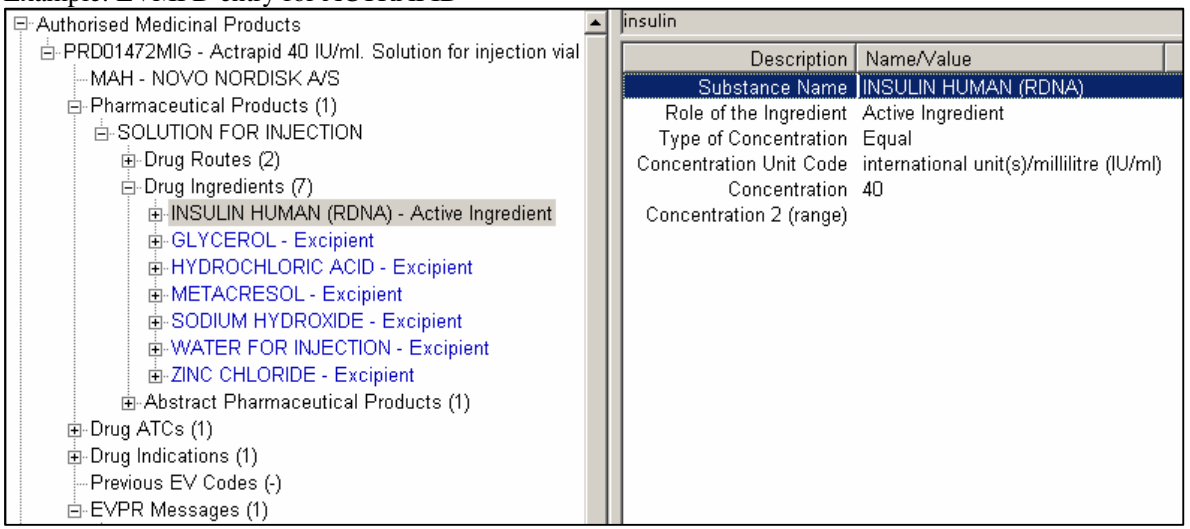
<tr><th>Date of Approval</th><th>Reference Number</th><th>Question</th><th>Answer</th></tr>
<tr><td></td><td></td><td></td><td>For a full list of excipients, see section 6.1

SmPC Section 6.1: ‘LIST OF EXCIPIENTS’
Zinc chloride
Glycerol
Metacresol
Sodium hydroxide or/and hydrochloric acid (for pH adjustment)
Water for injections

Example: EVMPD entry for ACTRAPID
 
</td></tr>
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			Example 2: SmPC INSULATARD (Insulin Medicinal Product containing an Insulin Formulation) SmPC Section 1: 'NAME OF THE MEDICINAL PRODUCT' Insulatard 40 IU/ml Suspension for injection in a vial SmPC Section 2: 'QUALITATIVE AND QUANTITATIVE COMPOSITION' Insulin human, rDNA (produced by recombinant DNA technology in Saccharomyces cerevisiae). 1 ml contains 40 IU of insulin human (…) Insulatard is a suspension of isophane (NPH) insulin For excipients, see Section 6.1 List of excipients. SmPC Section 6.1: 'LIST OF EXCIPIENTS' Zinc chloride Glycerol Metacresol Phenol Disodium phosphate dihydrate Sodium hydroxide or/and hydrochloric acid (for pH adjustment) Protamine sulphate Water for injections

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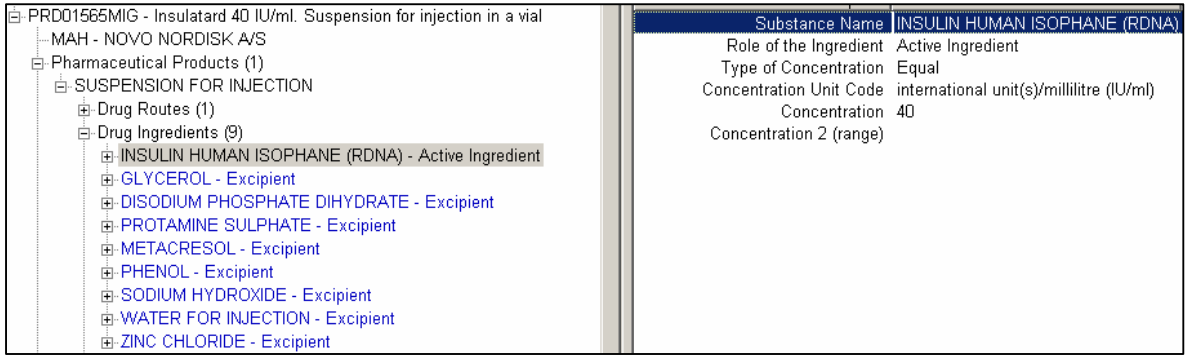
			Example: EVMPD entry for INSULATARD  Example 3: SmPC MIXTARD (Insulin Medicinal Product containing combination of insulin substance and/or formulation) SmPC Section 1: 'NAME OF THE MEDICINAL PRODUCT' Mixtard 30, 40 IU/ml Suspension for injection in a vial SmPC Section 2: 'QUALITATIVE AND QUANTITATIVE COMPOSITION' Insulin human, rDNA (produced by recombinant DNA technology in Saccharomyces cerevisiae). 1 ml contains 40 IU of insulin human (…) Mixtard is a mixture of dissolved insulin and isophane (NPH) insulin. Mixtard 30 consists of 30% dissolved insulin and 70% isophane insulin. SmPC Section 6.1: 'LIST OF EXCIPIENTS' Zinc chloride

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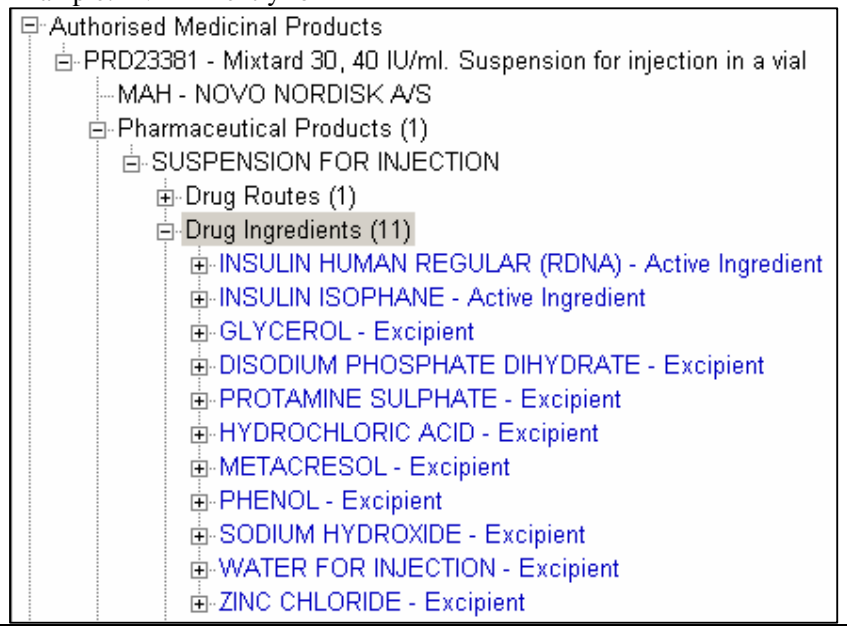
Date of Approval	**Reference Number**	**Question**	**Answer**
			Glycerol Metacresol Phenol Disodium phosphate dihydrate Sodium hydroxide or/and hydrochloric acid (for pH adjustment) Protamine sulphate Water for injections Example: EVMPD entry for MIXTARD 

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Dec-2007	ID: 017	What needs to be taken into account in populating the EVMPD as regards radioactive compounds? Which EVMPD field should be populated?	In addition to the information on the EudraVigilance Medicinal Product Dictionary (EVMPD) population, as described in the 'EVMPD training material', specific topics related to radioactive compounds only should be taken into account as follows: **a.** In accordance with section 1 'Name of the medicinal product' of the Summary of Product Characteristics (SmPC) or the Clinical Trial Application Form: - The medicinal product name should be entered in the EVMPD field 'Full Presentation Name' **b.** In accordance with section 2 'Qualitative and quantitative composition' of the Summary of Product Characteristics (SmPC) or the Clinical Trial Application Form: - The active ingredient should be entered in the EVMPD field 'Drug Ingredient' i. The EVMPD field 'Role of Ingredient' should be set to 'Active Ingredient' ii. For each active ingredient a separate substance name field should be populated iii. The substance name should be described based on the INN iv. Where no INN is assigned to the radioactive compound, the substance name should refer to the title of the relevant European Pharmacopoeia monograph, where one exists as followed: Example: European Pharmacopoeia monograph: Technetium 99mTc succimer injection EVMPD should be populated with Technetium (99mTc) succimer v. In cases where there is no European Pharmacopoeia monograph, the stylistics and precedents of European Pharmacopoeia monographs should be observed. vi. The substance name should be structured based on the following elements and the order of the elements should be followed: - Radionuclide - Isotope number - Element symbol - Carrier agent name vii. The EVMPD contains a look-up of titles of the monograph for radioactive compounds, as

<table>
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<tr><th>Date of Approval</th><th>Reference Number</th><th>Question</th><th>Answer</th></tr>
<tr><td></td><td></td><td></td><td>described in European Pharmacopoeia, which is systematically updated by the EMEA.
viii. If an appropriate term cannot be found in the EVMPD look-up, the MAH/sponsor of clinical trials should contact the EudraVigilance Helpdesk to obtain guidance on how the common name should be presented.

c. In accordance with section 6.1 ‘Excipients’ of the Summary of Product Characteristics (SmPC):
- Excipients should be entered in the EVMPD field ‘Drug Ingredient’
i. The EVMPD field ‘Role of Ingredient’ should be set to ‘Excipient’
ii. The strength/concentration of the excipient is not required
iii. For each excipient a separate substance name field should be populated

Example: SmPC CARDIOLITE®
CARDIOLITE®, Sections 1, 2 and 6.1 of SmPC:

Section 1. NAME OF THE MEDICINAL PRODUCT

CARDIOLITE®, Kit for the preparation of Technetium Tc-99m Sestamibi.

Section 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<u>1 vial contains</u>

<u>Active ingredients</u>
Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) Tetrafluoroborate 1.0 mg
Stannous chloride dihydrate 0.075 mg
L-Cysteine hydrochloride monohydrate 1.0 mg
Section 6.1. LIST OF EXCIPIENTS

Sodium citrate dihydrate
Mannitol</td></tr>
</table>

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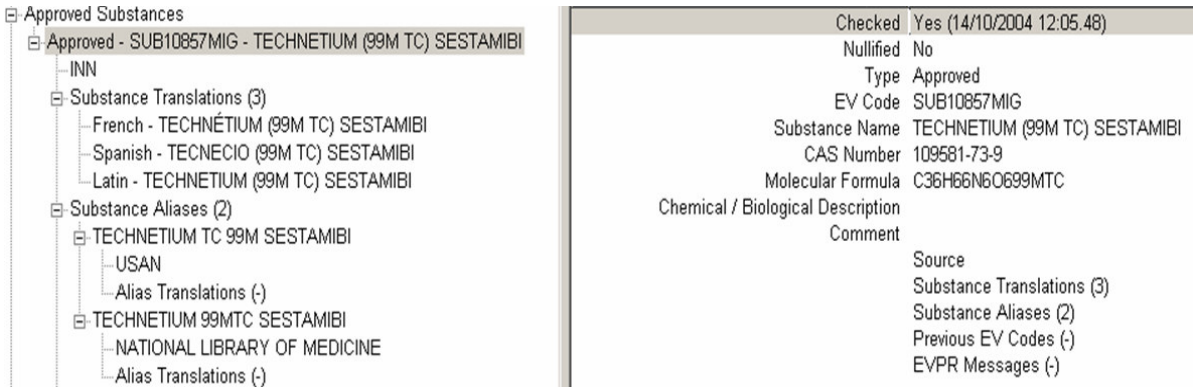
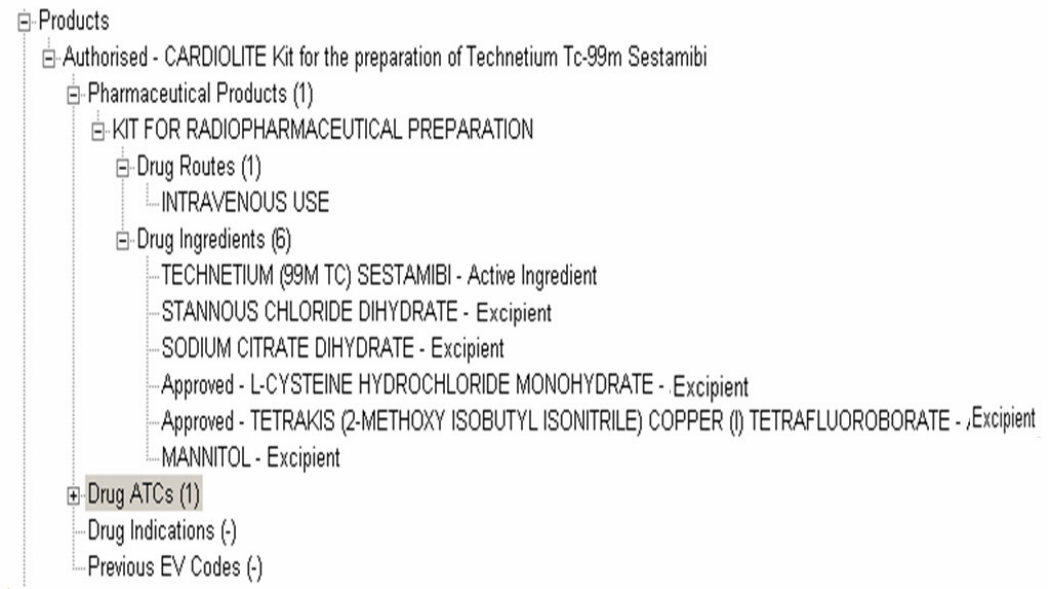
			Example: EVMPD entry for Technetium (99mTc) Sestamibi 

Questions and Answers related to Volume 9A			
Date of Approval	**Reference Number**	**Question**	**Answer**
			Example: EVMPD entry for CARDIOLITE® 
Dec-2007	ID: 018	What needs to be taken into account in populating the EVMPD as regards immunoglobulins? Which EVMPD field should be populated?	In addition to the information on the EudraVigilance Medicinal Product Dictionary (EVMPD) population, as described in the 'EVMPD training material', specific topics related to immunoglobulins only should be taken into account as follows: **a.** In accordance with section 1 'Name of the medicinal product' of the Summary of Product Characteristics (SmPC) or the Clinical Trial Application Form: - The medicinal product name should be entered in the EVMPD field 'Full Presentation Name' **b.** In accordance with section 2 'Qualitative and quantitative composition' of the Summary of Product

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			Characteristics (SmPC) or the Clinical Trial Application Form: - The active ingredient should be entered in the EVMPD field 'Drug Ingredient' i. The EVMPD field 'Role of Ingredient' should be set to 'Active Ingredient' ii. For each active ingredient a separate substance name field should be populated iii. The common name should be described based on the INN iv. Where no INN is assigned to the immunoglobulin, the common name should refer to the title of the relevant European Pharmacopoeia monograph, where one exists. In cases where there is no European Pharmacopoeia monograph, the stylistics and precedents of European Pharmacopoeia monographs should be observed. v. The common name should be structured based on the following elements and the order of the elements should be followed: - Extractive origin - Targeted antigen - Immnoglobulin - Intended use acronym (optional)* *The Intended use acronym refers to the abbreviation for the route of administration when stated in the reference source. For example, the EU Ph. comprises two distinct monographs for Human Normal Immunoglobulin: 1. Human Normal Immunoglobulin 2. Human Normal Immunoglobulin for intravenous administration These entries should be entered in the EVMPD as: 1. Human Normal Immunoglobulin 2. Human Normal Immunoglobulin (IV) vi. The EVMPD contains a look-up of titles of the monograph for immunoglobulins, as described in European Pharmacopoeia, which is systematically updated by the EMEA in collaboration with the CHMP BWP. vii. If an appropriate term cannot be found in the EVMPD look-up, the MAH/sponsor of clinical

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			trials should contact the EudraVigilance Helpdesk to obtain guidance on how the common name should be presented. **c.** In accordance with section 6.1 'Excipients' of the Summary of Product Characteristics (SmPC): - Excipients should be entered in the EVMPD field 'Drug Ingredient' i. The EVMPD field 'Role of Ingredient' should be set to 'Excipient' ii. The strength/concentration of the excipient is not required iii. For each excipient a separate field should be populated Example: SmPC RHOPHYLAC® **RHOPHYLAC®,** Sections 1, 2 and 6.1 of SmPC: Section 1. NAME OF THE MEDICINAL PRODUCT **RHOPHYLAC®** 300 micrograms / 2 ml, solution for injection in pre-filled syringe Section 2. QUALITATIVE AND QUANTITATIVE COMPOSITION **Human Anti-D immunoglobulin** Each 2 ml solution in pre-filled syringe contains: Human anti-D immunoglobulin 1500 IU (300 micrograms) Corresponding to a concentration of 750 IU (150 micrograms) per ml The product contains a maximum of 30 mg/ml of human plasma proteins of which 10 mg/ml is human albumin as stabiliser. At least 95 % of the other plasma proteins are IgG. Rhophylac contains not more than 5 micrograms/ml IgA. For a full list of excipients, see section 6.1 Section 6.1. LIST OF EXCIPIENTS Human albumin Glycine Sodium chloride

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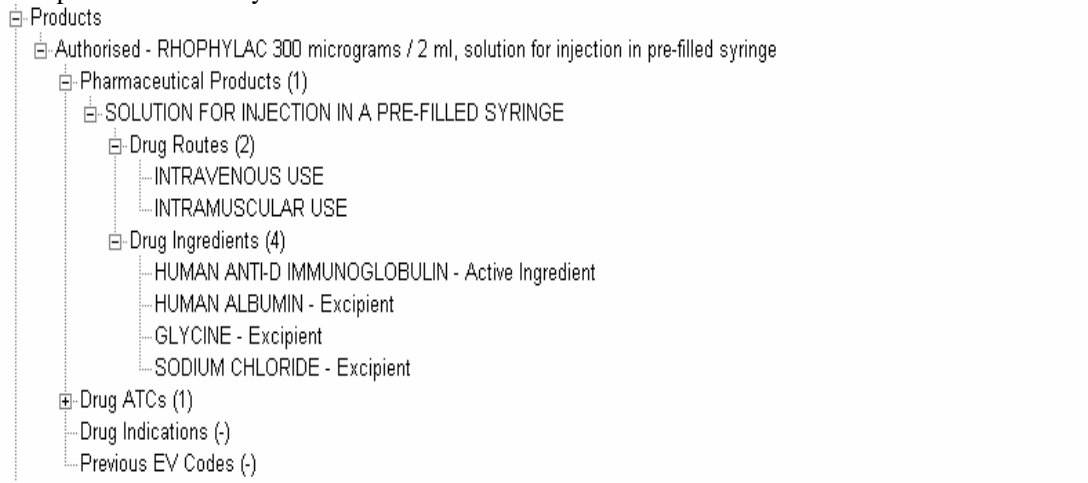
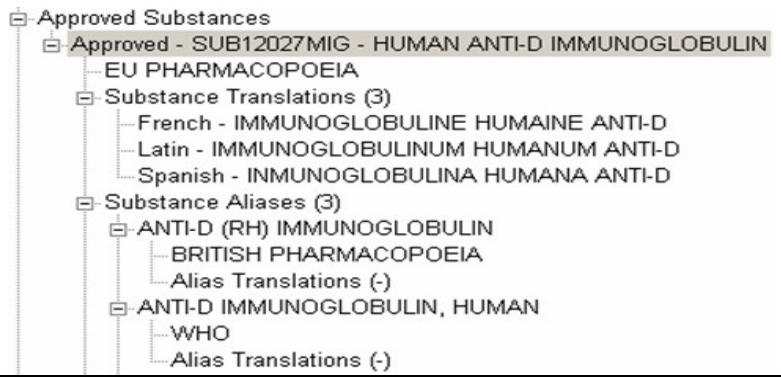
			Example: EVMPD entry for RHOPHYLAC®  Example: EVMPD entry for Human Anti-D Immunoglobulin 

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May-2008	ID: 019	What is the current status of the electronic reporting of ICSRs in Spain? Are there any specific local requirements that need to be followed?	The Spanish Medicines and Healthcare Products Agency (Agencia Española de Medicamentos y Productos Sanitarios – AEMPS) is reporting ICSRs electronically to EVPM since August 2007. MAHs should therefore no longer send ICSRs occurring in Spain (regardless of the authorisation procedure) to EVPM to avoid duplication. The AEMPS will contact those pharmaceutical companies, which have requested to initiate the testing of the electronic transmission of ICSRs. Detailed requirements are provided in the document "Update on electronic transmission of suspected individual case safety reports to the Spanish Medicines and Healthcare Products Agency", English version 2, dated 16th Jan 2008, which is published at the following website: http://www.agemed.es/actividad/documentos/infoInteres/docs/NI_XML_v2_Ingles.pdf The following aspects are nevertheless highlighted: **Data element ICH E2B(R2) A.1.1 *'Identification of the country of the primary source'*** Only Spain (ES) will be accepted as country for this field. A warning in the acknowledgement message will be generated for any ICSRs coming from a different country. Two different warnings will be generated. Where the country is an EEA member state other than Spain, the warning will inform the sender to send the ICSR to the correct country. Where the country is not an EEA member state, the warning will inform the sender to send the ICSR to EudraVigilance. **Data element ICH E2B(R2) A.2.1.2e *'Reporter's state'*** At least one of the data elements ICH E2B(R2) A.2.1.2e *'Reporter's state'* or ICH E2B(R2) A.2.1.2f *'Reporter's postcode'* should be populated. The Autonomous Community reported in the data element ICH E2B(R2) A.2.1.2e '*Reporter state'* is identified by 19 numerical codes. When ICH E2B(R2) A.2.1.2e '*Reporter state'* does not correspond with the Autonomous Community where the city/town is located, an error message will be generated and the ICSR will be rejected.

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			Data element ICH E2B(R2) A.2.1.2f *'Reporter's postcode'* At least one of the data elements ICH E2B(R2) A.2.1.2e *'Reporter's state'* or ICH E2B(R2) A.2.1.2f *'Reporter's postcode'* should be populated. The value in the data element ICH E2B(R2) A.2.1.2f *'Reporter's postcode'* should be the city/towns INE code. This is an alphanumerical code with 6 digits. The city/towns INE code is considered more useful than postcode because it allows classification by regions and cases will be forward to the concerned Regional Pharmacovigilance Centre. Spanish legislation requests that cases are sent to the concerned Regional Pharmacovigilance Centre. Where both data elements ICH E2B(R2) A.2.1.2e *'Reporter's state'* and ICH E2B(R2) A.2.1.2f *'Reporter's postcode'* are populated and data element ICH E2B(R2) A.2.1.2e does not correspond with the Autonomous Community where the city/town is located, an error message will be generated and the ICSR will be rejected. **Language requirements** Regarding the language requirements, the following ICH E2B(R2) data elements should be reported in Spanish or in English or both where possible. The original reported verbatim should always be clearly stated. ICH E2B(R2) A.1.8.2 *'List of documents held by sender'* ICH E2B(R2) A.1.13.1 *'Reason for nullification'* ICH E2B(R2) A.2.3.1 *'Study name'* ICH E2B(R2) B.1.7.1g *'Structured information on relevant medical history and concurrent conditions: Comments'* ICH E2B(R2) B.1.7.2 *'Text for relevant medical history and concurrent conditions (not including reactions)'* ICH E2B(R2) B.1.10.7.1g *'Structured information on relevant medical history and concurrent conditions of parent: Comments'* ICH E2B(R2) B.1.10.7.2 *'Text for relevant medical history and concurrent conditions of parent (not including reaction)'* ICH E2B(R2) B.2.i.0 *'Reaction/events as reported by primary source'* ICH E2B(R2) B.3.2 '*Results of test and procedures relevant to the investigation'* ICH E2B(R2) B.4.k.6 *'Drug Dosage text'* ICH E2B(R2) B.4.k.19 *'Additional information on drug'* ICH E2B(R2) B.5.1 *'Case narrative, including clinical course, therapeutic measures, outcome and additional relevant information'*: The case narrative should include a short description of the case in both Spanish and

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			English. ICH E2B(R2) B.5.2 *'Reporter's comment'* ICH E2B(R2) B.5.4 *'Sender's comments'*
May-2008	ID: 020	The completion of the EudraVigilance Interface for RMPs is not mentioned in Volume 9A. Is this a requirement? Has EMEA set any deadline for MAHs to comply with the completion of the electronic form for RMPs?	In accordance with Regulation (EC) 726/2004 and Directive 2001/83/EC as amended, applicants and marketing authorisation holders should provide a description of their risk-management system, where applicable. The aim of a risk-management system is to ensure that, by reducing or preventing risks, the benefits of the medicine or group of medicines concerned exceed the risks by the greatest achievable margin, for the individual patient and for the target population as a whole. Volume 9A of The Rules Governing Medicinal Products in the European Union provides guidance for the description of a Risk Management System, which should be provided in the form of an EU Risk Management Plan (EU-RMP). To aid consistency of the format and content of such plans, an EU-RMP template is provided in Annex 5.1.1 of Volume 9A. Annex 1 of this EU-RMP template refers to an additional template, which is acting as interface between the EU-RMP and EudraVigilance and should be completed for all EU-RMPs for medicinal products that are authorised through the centralised procedure. The data elements to be provided in electronic format can be found together with the EU-RMP template and the EU-RMP Annex 1 on the EudraVigilance website: (http://eudravigilance.emea.europa.eu/human/EURiskManagementPlans.asp). For centrally authorised medicinal products, the EU-RMP Annex 1 reflecting the final version of the EU-RMP as agreed at the time of the initial Opinion and of any following Opinions referring to updates to the EU-RMP Safety Specification, is due to be submitted to EudraVigilance within 15 calendar days after receipt of the Opinion. The information should be consistent with the data provided in the EU-RMP. The completed EU-RMP Annex 1 (XML format) should be sent to h-eurmp-evinterface@emea.europa.eu or by physical media (CD-ROM) to: EudraVigilance

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			Post-Authorisation of Medicines for Human Use Pharmacovigilance and Risk Management European Medicines Agency (EMEA) 7 Westferry Circus, Canary Wharf London E14 4HB - United Kingdom
May-2008	ID: 021	Volume 9A, chapter I.4 Section 3.5 'Reports from Patients and Other Consumers' states that medically unconfirmed adverse reactions should not be reported to the Agency/EudraVigilance on expedited basis. However, sending of reports from patients and other consumers which occurred in Liechtenstein to EudraVigilance is a requirement in Volume 9A.	To facilitate at national level the technical implementation of the electronic transmission of ICSRs by marketing authorisation holders, Liechtenstein has agreed with the EMEA that the Agency will provide Liechtenstein with access to EudraVigilance. In view of this agreement, reports from patients and other consumers that are medically unconfirmed and that refer to adverse reactions, which occurred in Liechtenstein, should be reported to the EudraVigilance Post-Authorisation Module in line with the requirements laid down in Volume 9A. As regards the reporting of these ICSRs, the ICH E2B(R2) data element (A.2.1.4) Primary Source *'Qualification'* should be populated with 'Consumer or other non health professional' and the ICH E2B(R2) data element (A.1.14) *'Was the case medically confirmed, if not initially from a health professional?'* should be populated with 'No'.
May-2008	ID: 022	MAHs receive an increasingly amount of ADRs from new sources of information such as e-mails, internet websites or virtual chartrooms sponsored by MAHs.	To be valid, a spontaneous case report must have a suspected drug, a suspected ADR, an identifiable (real) patient and also an identifiable reporter. Follow-up information is often required, ideally from a patient's treating physician; there is insufficient experience to know whether suitable follow-up is more or less difficult for Internet reports compared to those from other sources. It is particularly important to check the credentials of the reporter; this is sometimes difficult if not impossible without direct contact, e.g., by telephone. According to Volume 9A, Chapter I.4 Section 3.3, Marketing Authorisation Holders should consider utilising their

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		Since the identification of the source of information can be difficult, what is acceptable and what is not?	websites to facilitate adverse reaction collection, e.g. by providing adverse reaction forms for reporting or by providing appropriate contact details for direct communication. The CIOMS Working Group ('Current Challenges in Pharmacovigilance: Pragmatic Approaches – Report of CIOMS Working Group V". CIOMS. Geneva 2001') does not believe it necessary for regulators or companies routinely to "surf" the Internet beyond their own sites for individual spontaneous reports. However, it would be appropriate to look actively for ADR information on special home pages such as those of patient support or special disease groups if there is a significant issue (for example, new important signal, off-label use, circumstances leading to misinformation). It is also recommended that such sites be visited selectively for discussions on a significant drug safety issue in order to determine whether potentially useful safety information has been overlooked or whether information has been adequately communicated (i.e., to guard against misinformation).
May-2008	ID: 023	Can a marketing authorisation be granted if the Applicant has not yet applied for registration as EudraVigilance User?	The registration with Eudravigilance is part of the Detailed Description of Pharmacovigilance Systems and should be obtained as soon as possible. This should be followed in a two steps approach: 1. Registration procedure 2. Completion of the testing procedure. The successful testing of the electronic reporting to Eudravigilance should be completed prior to the granting of the Marketing Authorisation. Particularly since the medicinal product information that needs to be provided in Annex 1 of the EU-Risk Management Plan requires an access to the EudraVigilance Medicinal Product Dictionary (EVMPD). Moreover, in accordance with Regulation (EC) 726/2004 and Directive 2001/83/EC as amended, the Marketing Authorisation Holder of a medicinal product authorised in the EEA, save in exceptional circumstances, shall be able to report adverse reactions electronically to the Agency and the National Competent Authorities.

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May-2008	ID: 024	What are the rules governing submission of the retrospective transmission of data to the EMEA?	The retrospective electronic population of the EVPM is covered in Chapter III.11 Section 4 of Volume 9A of The Rules Governing Medicinal Products in the European Union. ▪ As a general principle, the MAH should transmit all cases, which originate from outside the EEA, to EVPM. These cases refer to spontaneous reports of serious cases and non-interventional trials. ▪ NCAs in the EU should provide all spontaneous reports of serious cases and non-interventional trials that occurred in their territory. Where no electronic reports or only limited data are available in structured format by NCAs, those NCAs should see to it that the data are entered in EVPM. In practice this means, that NCAs may ask MAHs to transmit the cases that occurred in their territory, to EVPM on their behalves
May-2008	ID: 025	How should the retrospective transmission of ICSRs be performed? 1. Should the data be in accordance with the ICH E2B(R2) standard? 2. Is it necessary to complete all data element required for ICH E2B(R2) submission?	It is important that retrospectively submitted ICSRs are flagged in the ICH M2 message header data element M.1.1 *'Message Type'* as 'backlog' ('ichicsr' should NOT be used so that the retrospective cases are excluded from the 15 days expedited compliance monitoring). The field value is case-sensitive and should be reported in lower case. All 'backlog' messages should be addressed to the message receiver identifier 'EVHUMAN'. 1. The retrospective electronic population of EVPM should follow the applicable ICH standards and guidelines referred to in Chapter III.2 of Volume 9A. As a general principle, the information available to the sender on the case should be provided in the ICSR format based on the ICH E2B(R2) data elements and message specifications, including the medical information coded in MedDRA version 4.0 or higher. 2. As with the prospective transmission, not all ICH E2B(R2) data elements have to be populated, only those for which you have structured data available in your local pharmacovigilance database. However, the cases must contain at least the minimum reporting criteria: a reporter, a patient, a suspect drug and a reaction. They should also contain a case narrative (ICH E2B(R2) data element B.5.1) in English, in accordance with the guidance in Volume 9A, Chapter III.11 Section 5. A detailed description of the E2B(R2) data elements generating error messages for the electronic transmission of ICSRs is presented in Appendix A of the Note for Guidance EudraVigilance Human Version 7.0 Processing of

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Date of Approval	**Reference Number**	**Question**	**Answer**
			Safety Messages and Individual Case Safety Reports (ICSRs), Doc. Ref. EMEA/H/20665/04/final.
May-2008	ID: 026	In accordance with Volume 9A, organisations were requested to submit cases retrospectively by 1st Feb 2008. What are the steps to follow when this deadline has not been reached?	Any organisation that was not able to meet the 1st February 2008 target date for the retrospective transmission of ICSRs as outlined in Volume 9A Chapter III.11 Section 4 should inform the Agency as soon as possible. The contact point for this is Tom Paternoster (tom.paternoster@emea.europa.eu). You should provide a high level plan as regards the expected date of initiation of the retrospective transmission of ICSRs by your organisation, an estimate of the volume of the cases to be transmitted and the planned date of completion.
May-2008	ID: 027	How should organisations proceed once they are ready to perform the retrospective transmission of data to the EMEA?	As stated in Volume 9A, Chapter III.11 Section 4.1 the sender of retrospectively transmitted ICSRs – as described in Chapter III.11 Section 4 – should perform some initial testing with the Agency, using the EudraVigilance test environment (EVTEST) before transmitting the retrospective ICSRs to the production environment of EVPM. The contact point for the testing is Nick Halsey (nick.halsey@emea.europa.eu). A small number of test ICSRs should be transmitted to ensure that they will not be rejected by EVPM and that the criteria are met as outlined in Volume 9A, Chapter III.11 Section 4.1. Once the testing has been successfully completed, or if you are transmitting via the EVWEB online forms, you should contact Tom Paternoster (tom.paternoster@emea.europa.eu), informing him of when you will be ready to initiate the retrospective transmission of ICSRs. You should agree on a plan as regards the expected date of initiation of the retrospective transmission of ICSRs by your organisation, an estimate of the volume of the cases to be transmitted and the planned date of completion.
May-2008	ID: 028	What are the reporting criteria to retrospectively transmit ISCRs originating in Member States, who joined the EU since 1st of May 2004?	With regard to the Member States who joined the EU since 1st May 2004, MAHs should provide all spontaneous reports of serious cases and non-interventional studies for the period of 1 January 1995 until the date of accession. For example, for those Member States, which joined the EU on the 1st May 2004, the MAHs should retrospectively transmit the ICSRs for those countries covering the period from 1st January 1995 to 30 April 2004. In the case of Romania and Bulgaria, which joined the EU on 1st January 2007, MAHs should retrospectively transmit the ICSRs for these countries covering the period from 1st January 1995 to 31 December 2006.

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May-2008	ID: 029	How should reports from consumers be handled when they include medical documentation?	When a consumer submits medical documentation that supports the occurrence of a suspected serious adverse drug reaction to an identifiable patient and which indicates that an identifiable healthcare professional suspects a causal relationship between a medicinal product and the reported serious adverse drug reaction, this should be considered as a medically confirmed report which fulfils expedited reporting requirements. In addition, ▪ Attempt should be made to obtain additional information from the healthcare professional. ▪ The ICSR should be reported electronically in expedited manner no later than 15 calendar days of receipt of the initial information from the consumer. ▪ The data element ICH E2B(R2) A.1.14 '*Was the case medically confirmed,* ***if not initially*** *from a health professional?'* should be populated with the value '1' (yes). ▪ Other guidance reported in Volume 9A, Chapter I.4 Section 3.5 'Reports from Patients and Other Consumers' applies. For some reactions, the documentation in laboratory data or tests supports the suspicion and does not require additional medical clarification.
May-2008	ID: 030	Should a case be reported, where a primary source/reporter has indicated that a serious adverse drug reaction occurred but has not specified the actual adverse reaction?	In line with Volume 9A, Chapter I.4 'Requirements for Expedited Reporting of Individual Case Safety Reports', the MAH is expected to validate all adverse reactions reported by a healthcare professional to ensure, prior to reporting to the Competent Authorities, that the minimum information required is included in the report: ▪ **An identifiable healthcare professional reporter** (Section A.2 *'Primary source(s) of information'* of ICH E2B(R2)) (see Annex 4 of Volume 9A); The reporter may be identified by name or initials, address or qualification (e.g. physician, dentist, pharmacist, nurse), taking into account EU legislation on data protection (Directive 95/46/EC, Regulation (EC) No 45/2001) and relevant national legislation (see also Chapter III.5 Section 4 of Volume 9A). Contact details for a healthcare professional should be available for the reporter to be considered as identifiable. ▪ **An identifiable patient** (Section B.1 *'Patient characteristics'* of ICH E2B(R2)); The Patient may be identified by initials, patient number, date of birth, age, age group or sex. The information should be as complete as possible, taking into account EU legislation on data protection (Directive 95/46/EC, Regulation (EC) No 45/2001) and relevant national legislation (see also Chapter III.5 Section 4 of Volume 9A).

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			▪ **At least one suspected active substance/medicinal product** (Section B.4 'Drug(s) information' of ICH E2B(R2)); ▪ **At least one suspected adverse reaction** (Section B.2 *'Reactions(s)/event(s)'* of ICH E2B(R2)). In this case, it is considered that the fourth element of information (i.e., a suspected adverse reaction) required to submit this serious report on an expedited basis is missing. Therefore this type of report should not be submitted on an expedited basis to the Competent Authorities. The report should be followed-up to obtain all required minimum information relevant to the case. Where relevant follow-up information is obtained, which clarifies the reported adverse reaction, the report should be sent electronically to the Competent Authorities on an expedited basis according to the requirements described in Chapter I.4 of Volume 9A and the following rules should be applied: ▪ The ICH E2B(R2) A.1.6b data element *'Receive date'* should contain the date of receipt of the initial report; ▪ The ICH E2B(R2) A.1.7b data element *'Receipt date'* should contain the date of receipt of the follow-up report where all four minimum information required to fulfil reporting criteria were made available. ▪ Clarification should be provided in the ICH E2B(R2) B.5.1 data element '*Case narrative including clinical course, therapeutic measures, outcome and additional relevant information*' that one of the four minimum information required to fulfil reporting criteria was missing in the initial report.
Sep-2008	ID: 031	Is a sponsor required to submit SUSARs to Ethic Committees and investigators if these SUSARs originate in non-interventional studies?	There is no specific requirement as regards the reporting obligation of the sponsor to the investigator for SUSARs originating in non interventional studies. According to Volume 9A, sponsors should follow the relevant national legislation in those member states where this exists.

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Sep-2008	ID: 032	A suspected serious adverse reaction occurred with a biosimilar medicinal product. How should the biosimilar medicinal product be reported in the ICH E2B(R2) section B.4 '*Drug(s) information*' of the ICSR?	When reporting a suspect serious adverse reaction related to a biosimilar medicinal product, the following ICH E2B(R2) data elements should be completed for the concerned product: ▪ The invented/common or scientific medicinal product name in the ICH E2B(R2) data element B.4.k.2.1 '*Proprietary medicinal product name'* ▪ The active substance name(s) in the ICH E2B(R2) data element B.4.k.2.2 *'Active substance name(s)*'; if there are multiple active substances, the ICH E2B(R2) data element B.4.k.2.2 should be repeated as necessary ▪ The batch/lot number in the ICH E2B(R2) data element B.4.k.3. *'Batch/lot number'* ▪ The name of the marketing authorisation holder in the ICH E2B(R2) data element B.4.k.4.3 '*Name of holder/applicant'* ▪ The applicable marketing authorisation number in the ICH E2B(R2) data element B.4.k.4.1 '*Authorization/Application Number'* If initially not available, the sender of the ICSR should make the necessary attempts to obtain all of the above information from the primary source.
Sep-2008	ID: 033	Company A holds marketing authorisations for six influenza vaccines. Five medicinal products contain seasonal influenza strain and one medicinal product is a pandemic influenza vaccine. The qualitative composition of these medicinal products varies	In the frame of spontaneous reporting, a significant number of adverse reaction reports related to influenza vaccines do not contain information as regards e.g. the invented name, the exact seasonal composition or the batch number. MAHs should make all efforts to contact the primary source to obtain further information on the administered vaccine. If no further follow-up information can be obtained on the exact type of influenza vaccine (like strain, split, or inactivated vaccine type etc.) the adverse reaction still should be reported in line with the rules laid down in Volume 9A. The MAH should prepare **one** ICSR based on the information as reported by the primary source. There is no need to prepare an ISCR for all influenza vaccine products, for which the MAH holds a marketing authorisation. The MAH should report "Influenza Vaccine" as the active substance name in the ICH E2B(R2) data element

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		as follows: – Influenza vaccine (Split viron, inactivated) – Influenza vaccine (Surface antigen, inactivated) – Influenza vaccine (Surface antigen, inactivated, virosome) – Pandemic influenza vaccine (H5N1) (Split virion, inactivated, adjuvanted) Company A receives a report related to a suspected serious adverse reaction for an influenza vaccine without further specifications related to the medicinal product. How should Company A report the case taking into account that it holds marketing authorisations for six different influenza vaccines?	B.4.k.2.2 *'Active substance name(s)*'. It is further recommended that such cases, where the vaccine is not further specified, are summarised in the PSUR in a dedicated chapter.
Sep-2008	ID: 034	A MAH receives an adverse reaction report	If a MAH receives a report for a suspected serious adverse reaction, where a batch number is provided, and based on the batch number, the MAH can exclude that it is a medicinal product, for which he holds a marketing

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		related to a vaccine. The reported batch number does not match any batch numbers of those medicinal products for which the MAH has a marketing authorisation. Volume 9A does not mention the batch number as an exclusion criteria for safety reporting. Does the MAH need to report the case?	authorisation, the MAH does not need to report the ICSR. However, if it appears that the batch number is not reported correctly or completely (e.g. incomplete batch number), the MAH should make all efforts to contact the primary source to obtain further information on the reported batch number. If no further follow-up information can be obtained and the MAH cannot exclude with certainty that it is a medicinal product for which he holds a marketing authorisation, the adverse reaction should be reported in accordance with the reporting rules outlined in Volume 9A. The MAH should state in the ICH E2B(R2) data element B.5.1 '*Case narrative including clinical course, therapeutic measures, outcome and additional relevant information*' that the reported batch number might be incomplete or incorrect.
Sep-2008	ID: 035	Should a follow-up report received from a non-health care professional be submitted to EudraVigilance if the initial serious case has originally been received from a health care professional?	If the initial serious case has been originally medically confirmed, a follow-up report received from a non-health care professional should be submitted on an expedited basis. Any effort should be made to obtain medical confirmation of the new information. The MAH should state in the ICH E2B(R2) data element B.5.1 '*Case narrative including clinical course, therapeutic measures, outcome and additional relevant information*' that information in this follow-up report has been reported by a non-health care professional.
Sep-2008	ID: 036	Some NCAs require a translation of the case narrative in the local language. The current field length of	For ICSRs, where the case narrative in the ICH E2B(R2) data element B.5.1 '*Case narrative including clinical course, therapeutic measures, outcome and additional relevant information*' exceeds 20,000 characters, proceed as follows: – Create a document in PDF format which contains the case narrative 'overflow'.

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		the ICH E2B(R2) data element B.5.1 '*Case narrative including clinical course, therapeutic measures, outcome and additional relevant information*' is limited to 20.000 characters. How should the translation be reported in ICSRs? The limit may be reached with complex legal cases for example. For most MAHs it is too costly and resource intensive to have different versions of the same narrative appearing in the ICH E2B(R2) data element B.5.1 to satisfy all authorities.	– The document should contain a reference to the applicable *'Worldwide unique case identification number'* (ICH E2B(R2) A.1.10.1 or A.1.10.2) and a reference to the *'Date of receipt of the most recent information for this report'* (ICH E2B(R2) A.1.7) of the corresponding ICSR. – The file name of the PDF document with the case narrative overflow should match exactly the *'Worldwide Unique Case Identification Number'* (ICH E2B(R2) A.1.10.1 or A.1.10.2 as applicable) of the corresponding ISCR. – If there is a follow-up for the individual case, the PDF file name with the Worldwide Unique Case Identification Number should be maintained but should include a sequence number separated with a dash. *Example:* *ICSR: ES-ORGABC-23232321 (ICH E2B(R2) data element A.1.10.1 'Worldwide Unique Case Identification Number');* *File name: ES-ORGABC-23232321.pdf.* *Follow-up information:* *ICSR: ES-ORGABC-23232321 (ICH E2B(R2) data element A.1.10.1 'Worldwide Unique Case Identification Number' remains unchanged;* *File name: ES-ORGABC-23232321-1.pdf*
Sep-2008	ID: 037	Is the use of an official Community language other than English permitted to populate the medicinal product name fields in the EVMPD?	The name of the medicinal product refers, according to Volume 2A 'Procedures for Marketing Authorisation', either to a single invented name or a common or scientific name (when available, the International Non-Proprietary Name of the active substance(s)) accompanied by a trade mark or the name of the marketing authorisation holder). The name of the medicinal product should be entered in the EVMPD as stated in the Summary of Product Characteristics, in the local language, but **using the Latin character set**.

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			Example 1: Venlafaxine Liconsa 225 mg Tabletka o przedłużonym uwalnianiu *- Full Presentation Name: Venlafaxine Liconsa 225 mg Tabletka o przedluzonym uwalnianiu* *- Product Short Name: Venlafaxine* *- Product Generic Name: (not applicable)* *- Product Company Name: Liconsa* *- Product Strength Name: 225 mg* *- Product Form Name: Tabletka o przedluzonym uwalnianiu* Example 2: Mycamine 50 mg κόνις για διάλυμα προς έγχυση - Full Presentation Name: Mycamine 50 mg conis gia dialima pros eghisi - Product Short Name: Mycamine - Product Generic Name: (not applicable) - Product Company Name: (not applicable) - Product Strength Name: 50 mg - Product Form Name: conis gia dialima pros eghisi For all other EVMPD fields (*Substance, Pharmaceutical Form, Administration Route, Concentration)* English should be used. In addition, for the *Substance* related fields in the EVMPD (*Substance Translation* and *Alias Translation*), translations for all Community languages can be added. As regards electronic adverse reaction reporting to EudraVigilance, the medicinal product name in the ICH E2B(R2) data element B.4.k.2.1 '*Proprietary medicinal product name*' should be provided in line with EVMPD 'Full Presentation Name' or 'Product Short Name'. This will allow for the ICSR to be recoded automatically against the EVMPD.