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EudraLex – Volume 9A – Questions and answers on implementation

Version 5.4

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This document supersedes document version 3.2 published in October 2008 (EMEA/560457/2008). New questions and answers (numbers 038 to 064) have been included.

Keywords	Frequently asked implementation questions in relation to EudraLex - Volume 9A of the Rules Governing Medicinal Products in the European Union, applicable to all stakeholders exchanging Individual Case Safety Reports (ICSRs) electronically within the EEA.

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Executive summary

The EudraVigilance Expert Working Group (EV-EWG) and the EudraVigilance Steering Committee, in consultation with the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP), have developed a series of questions and answers (Q&As) to address frequently asked implementation questions from stakeholders in relation to EudraLex - Volume 9A of the Rules Governing Medicinal Products in the European Union: Pharmacovigilance for Medicinal Products for Human Use.

This Q&A document provides conventions for the harmonised interpretation of EudraLex - Volume 9A. Stakeholders, e.g. marketing-authorisation holders (MAHs), national competent authorities (NCAs), vendors and contract research organisations, can submit implementation-related questions to the EV-EWG. Questions can be submitted by e-mail to: eudravigilance@ema.europa.eu

Answers to these questions are developed by the EV-EWG in consultation with the PhVWP based on a consensus process.

The Q&As addressed within this document are presented in relation to the relevant chapters in EudraLex - Volume 9A.

- Questions 1 to 18 were initially published in the Q&As document version 1.2 in February 2008 (EMEA/111972/2008).
- Questions 19 to 37 were included in October 2008 and published in the Q&As document version 3.2 (EMEA/560457/2008).
- Questions 38 to 64 are a new set of Q&As. They are presented in blue in this document (version 5.4, EMA/46003/2011).

Part I Chapter 1: General Principles – *Roles and Responsibilities of the Marketing Authorisation Holder and the Qualified Person for Pharmacovigilance*

Reference number	Questions	Answers
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 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, saved in exceptional circumstances, shall be able to report adverse reactions electronically to the Agency and the National Competent Authorities.
ID: 044	Should the server with the Pharmacovigilance database be located in the EEA? Should the actual data entry of the adverse events be performed in the EEA?	In line with EudraLex - Volume 9A, Chapter I.1 section 2 (Roles and Responsibilities of the Marketing Authorisation Holder and the Qualified Person Responsible for Pharmacovigilance), it is not specifically required for the pharmacovigilance database neither for the processing of the Individual Case Safety Reports (ICSRs) to be located or performed within the EEA. However the Qualified Person Responsible for Pharmacovigilance (QPPV), who should reside in the EEA, should have an oversight of the pharmacovigilance system in terms of structure and performance. The QPPV should be in a position to guarantee either directly or through supervision "the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the MAH and to the medical representatives, is collected and collated in order to be accessible at least at one point within the EEA."
ID: 045	What is requested in terms of re-testing when company databases are	To assure the successful operation of Electronic Data Interchange (EDI), each new EDI partner who wishes to transmit Safety Messages electronically needs to undergo a staged test procedure, which

Reference number	Questions	Answers
	upgraded or modified?	is described in the 'Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance during the Pre- and Post-Authorisation Phase in the European Economic Area (EEA)' (Doc. Ref: EMEA/115735/2004). Any technical changes must be communicated immediately in writing between the EDI Partners. Major technical changes may require the re-initiation of the test phases. If a company is making minor changes to its system which will not affect XML message generation, there is no need to re-test with EudraVigilance (EV). However if the changes may affect the XML message generation (either altering the fields which populate the XML message or the extraction of data from the database itself) then the company will need to re-test with EV. To initiate the re-testing or for any questions, emails should be sent to eudravigilance@ema.europa.eu.

Part I Chapter 3: Requirements for Risk Management Systems – *EU Risk Management Plan (EU-RMP)*

Reference number	Questions	Answers
ID: 020	The completion of the EudraVigilance Interface for Risk Management Plans (RMPs) is not mentioned in EudraLex - Volume 9A. Is this a requirement? Has EMA 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. EudraLex - Volume 9A 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 EudraLex - Volume 9A. Annex 1 of this EU-RMP template refers to an additional template, which is acting as an 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.ema.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 by secure email (via Eudralink) to h-eurmp-evinterface@ema.europa.eu.
ID: 048	Are MAHs expected to update MedDRA terms described in a submitted EU-Risk Management Plan with every release of MedDRA?	Companies are not requested to recode all the MedDRA terms when a new MedDRA version is released. However when an update of the EU-Risk Management Plan is submitted, the MedDRA terms should be recoded with the latest MedDRA version.

Part I Chapter 4: Requirements for Expedited Reporting of Individual Case Safety Reports – *Introduction*

Reference number	Questions	Answers
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 EudraLex - 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 EudraLex - 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 EudraLex - 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 EudraLex - Volume 9A). **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 in order 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 EudraLex - Volume 9A and the following rules should be applied:

Reference number	Questions	Answers
		- 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 the 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 the reporting criteria, was missing in the initial report.
ID: 043	How to interpret contactable reporter versus identifiable reporter? If a reporter is not contactable but the company knows the qualification of the reporter, does this mean that the reporter is not identifiable and the case is not a valid one?	As mentioned in EudraLex - Volume 9A, Chapter I.4, the MAH is expected to validate all adverse reactions reported by healthcare professionals to ensure, prior to reporting to the Competent Authorities, that the minimum information required is included in the report. This includes an identifiable reporter. The reporter may be identified by name or initials, address or qualification (e.g. physician, dentist, pharmacist or nurse), taking into account the EU legislation on data protection (Directive 95/46/EC, Regulation (EC) No 45/2001) and the relevant national legislation. In addition, the contact details for a Healthcare Professional should be available for the reporter to be considered as identifiable. If a healthcare professional does not wish to provide contact details while reporting adverse reactions to NCAs or MAHs, the report should still be considered as valid providing that it has been possible by the organisation who was informed of the case to ascertain it directly with the reporter.
ID: 054	A MAH is made aware by the medicinal product manufacturer of a reaction occurring with the concerned medicinal product. How should the case be handled when it occurs in a country where the MAH does not hold a marketing authorisation for the concerned medicinal product? Should the case be considered for expedited/ periodic reporting?	If the MAH does not hold a marketing authorisation in the country where the reaction occurred, the individual case safety report does not qualify for expedited reporting to the Competent Authorities, nor to EudraVigilance. However if the individual case safety report provides information that may lead to a change in the known benefit-risk balance for the medicinal product the MAH is responsible for, this possible change should be notified to the Competent Authorities without delay. Any relevant safety information which could affect the benefit-risk balance of the medicinal product should also be analysed in the corresponding PSUR.

Part I Chapter 4: Requirements for Expedited Reporting of Individual Case Safety Reports – Requirements by Reporting Source – *Spontaneous Reports from Health Professionals*

Reference number	Questions	Answers
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 EudraLex - Volume 9A, Chapter I.4 Section 3 'Requirements by reporting source' and 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 EudraLex - 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'.
ID: 034	A MAH receives an adverse reaction report 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. EudraLex - Volume 9A does not mention the batch number as an exclusion criteria for safety reporting. Does the MAH need to report the case?	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 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 EudraLex - 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.

Part I Chapter 4: Requirements for Expedited Reporting of Individual Case Safety Reports – Requirements by Reporting Source – *Reports Published in the Worldwide Literature*

Reference number	Questions	Answers
ID: 012	How should the requirements of EudraLex - 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 are 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 particular, clarification is needed, if the country where the case occurred can be used to exclude the ownership of the product?	In EudraLex - 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 worldwide 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.
ID: 039	Should literature search be performed at active substance or at product name(s) level?	As stated in Chapter I.4, section 3.2 of EudraLex - Volume 9A, the MAH is expected to maintain awareness of possible publications by accessing a widely used systematic literature review and reference database (e.g. Medline, Excerpta Medica or Embase) no less frequently than once a week. This should be performed by searching for the active substance(s) name(s) and for the marketed name(s) of the medicinal product the MAH is responsible for. **For the purpose of expedited reporting,** the MAH should identify cases of adverse reactions issued from spontaneous reports and non-interventional studies, and which are published in the scientific and medical literature, including relevant abstracts from meetings and draft manuscripts. Only valid ICSRs which qualify for expedited reporting should be reported and the following recommendations should be taken into account:

Reference number	Questions	Answers
		ICSRs should be excluded from expedited reporting if the MAH can assume that it is not one of its products the publication refers to on the basis of the active substance(s), formulation, route of administration and country of origin of the report. If the medicinal product source and/or the invented name is not specified and the ownership of the product cannot be excluded, the report should indicate, in the ICH E2B(R2) data element B.5.1 *'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information'* that the specific product source and/or the invented name was not identified; If multiple medicinal products are mentioned in the publication, a report should be submitted only by the MAH(s) of the product(s) which is (are) identified by the publication's author(s) as having at least a possible causal association with the adverse reaction. **For the purpose of periodic reporting,** any relevant published safety information which could affect the benefit-risk balance of the medicinal product should be analysed in the corresponding PSUR and publication reference(s) should be provided. MAHs should assess in the PSUR: Published case reports containing important safety findings related to the corresponding active substance(s) of the medicinal product under review in the PSUR. This concerns (i) serious ICSRs for which the company does not hold a marketing authorisation in the country where the reaction occurred and which have not been reported on an expedited basis, (ii) serious ICSRs which have been reported on an expedited basis, (iii) non-serious ICSRs, Published studies (interventional clinical trials and non-interventional studies) containing important safety findings (positive or negative) even if the company does not have a registration in the country where the study was conducted. Literature articles containing relevant safety findings assessed in the PSUR and which have not been reported on an expedited basis to the Competent Authorities should also be annexed to the PSUR.
ID: 040	Is it acceptable to carry out literature searches in several databases but Embase?	The MAH is expected to maintain awareness of possible publications related to the medicinal product it is responsible for by accessing a widely used systematic literature review and reference database no less frequently than once a week. The MAH should ensure that the searched literature review and reference databases contain the largest reference of articles in relation to the corresponding medicinal product properties.

Reference number	Questions	Answers
ID: 041	If a case is identified in a publication based on an analysis from a Competent Authority database, should it be submitted to the Competent Authority as a literature report?	A case identified in a publication based on analysis from a National Competent Authority (NCA) database in the EEA should not be submitted to EudraVigilance or to the NCA of the country of origin of the case. However, the case needs to be submitted to the Rapporteur/Reference Member State as applicable in line with the reporting rules of EudraLex - Volume 9A (Chapter I.4 section 3 'Requirements by Reporting Source'). Furthermore, the case might qualify for expedited reporting to NCAs in the EEA and EudraVigilance if it originates from outside the EEA. It should be taken into account that NCAs in the EEA have the obligation to inform the MAHs of any serious adverse reactions related to medicinal products for which they hold a marketing authorisation. Duplicates in the MAHs database should therefore be avoided. If the cases discussed in the publication also involve non-serious adverse reactions, this information should be also captured and reflected in the PSUR accordingly.
ID: 055	What are the expedited/periodic reporting requirements for cases identified in the scientific literature and originating in a country where a MAH holds a marketing authorisation but has never marketed the medicinal in this country?	In this situation, the same expedited and periodic reporting obligations as for a marketed medicinal product apply.
ID: 059	A new literature article contains detailed information on several individual cases which where published in the past by other authors. For example, an article published in 2008 describes a female who suffered from urticaria with the medicinal product X (Campos et al. 1989), a male who suffered from myocarditis with the medicinal product Y	In principle, the company A should already have identified these literature reports which are referenced in the new articles and individual cases should already have been created. If this is has not been done, the recommendations detailed in EudraLex - Volume 9A, Chapter I.4 Section 3.2 'Reports published in the worldwide literature' and in question ID 012 should be followed. Providing that the four minimum criteria are reported in the article and if ownership of the suspected medicinal products X and Y cannot be excluded by the company A on the basis of the active substance name, formulation, route of administration and primary source country, the company A should assume that it is one of its products the publication refers to and individual cases should be created from this article. The reports should indicate that the invented name was not identified if this information is not

Reference number	Questions	Answers
	(Andersen et al 1990). The company A owns marketing authorisation for the medicinal products X and Y in the countries where the reactions occurred. Is there a need for the company A to create retrospectively cases for those references included in the new literature articles?	available. The expedited reporting requirements described in Chapter I.4 of EudraLex - Volume 9A should be followed. However if the company A does not own a marketing authorisation in the primary source country, the company does not need to submit these cases on an expedited basis to the Competent Authorities in the EEA and to EudraVigilance.

Part I Chapter 4: Requirements for Expedited Reporting of Individual Case Safety Reports – Requirements by Reporting Source – *Information on Adverse Reactions from the Internet*

Reference number	Questions	Answers
ID: 022	MAHs receive an increasing amount of adverse drug reactions (ADRs) from new sources of information such as e-mails, internet websites or virtual chat-rooms sponsored by MAHs. Since the identification of the source of information can be difficult, what is acceptable and what is not?	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 EudraLex - Volume 9A, Chapter I.4 Section 3.3, Marketing Authorisation Holders should consider utilizing their 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 actively look for ADR information on special home pages such as those of patients support or special diseases groups in order to check 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).
ID: 047	A company identifies valid individual case safety reports on internet websites (such as 'blogs' and forum) but the minimum information for processing the cases is not available	In such situation, the country where the information was received should be used as the country of primary source.

Reference number	Questions	Answers
	e.g. the country of the primary source is missing. What convention should be used to provide the information regarding the country?	

Part I Chapter 4: Requirements for Expedited Reporting of Individual Case Safety Reports – Requirements by Reporting Source – *Reports from Organised Data Collection Systems*

Reference number	Questions	Answers
ID: 062	A company holds a marketing authorisation in the EEA for the medicinal product X. The company also holds active clinical trials in the EEA for the medicinal product X. What are the post-authorisation reporting requirements for cases of suspected expected serious adverse reactions - If the reactions originate in a clinical trial authorised in the EEA and are related to the medicinal product X? - If the reactions originate in a clinical trial not authorised in the EEA and are related to the medicinal product X?	In this scenario, the suspected expected serious adverse reactions occur in the context of a clinical trial as defined in the Directive 2001/20/EC and are to be reported according to this directive's rules (i.e. in the Annual Safety Report (ASR)). The post-authorisation reporting obligations for cases of suspected expected serious adverse reactions occurring in clinical trials and associated to authorised medicinal products under investigation concern only the reporting in the corresponding PSUR for the medicinal product X. The requirements described in Chapter I.6 of EudraLex - Volume 9A (Section 3.7 and Section 3.8) should be followed whether or not the clinical trial is authorised in the EEA: - The cases of suspected expected and unexpected serious adverse reactions should be presented as line listings and summary tabulations in the PSUR of the authorised medicinal product. - If the clinical trial yields safety information (including lack of efficacy data) with a potential impact on the authorised medicinal product, a discussion of any interim or final results should also be included in the "Study" Section of the PSUR. There is no post-authorisation expedited reporting obligation for cases of suspected expected serious adverse reactions occurring in interventional clinical trial and originating within or outside the EEA.
ID: 063	A company A holds marketing authorisations in the EEA for a medicinal product X. A sponsor B is using the medicinal product X in a clinical trial authorised in the EEA. The company A and the sponsor B have NO contractual agreement. The sponsor B is responsible for the expedited and	In this scenario, the cases do not qualify for expedited reporting by the company A to the concerned Competent Authorities, nor to EudraVigilance. In accordance with the Directive 2001/20/EC, only the sponsor B (or his designate) should report these cases of SUSARs. However if the cases provide information that may lead to a change in the known benefit-risk balance for the medicinal product X, this possible change should be notified to the Competent Authorities without delay by the company A. The company A should also analyse in the corresponding PSUR for the medicinal product X any safety information in relation to the reports of SUSARs, which could impact on the benefit-risk balance of the authorised medicinal product.

Reference number	Questions	Answers
	periodic reporting of serious reactions (SUSARs, ASRs/DSUR) occurring in the clinical trial. The company A receives from the sponsor B cases of Suspected Unexpected Serious Adverse Reactions (SUSARs) related to the medicinal product X and originating within the EEA. What are the reporting responsibilities for the company A regarding the aforementioned cases of SUSARs?	
ID: 064	A company A holds marketing authorisations in the EEA for a medicinal product X. A sponsor B is using the medicinal product X in a clinical trial authorised outside the EEA. The company A and the sponsor B have NO contractual agreement. The sponsor B has no authorised clinical trial in the EEA with the medicinal product X. The sponsor B has no expedited and periodic reporting obligations in the EEA. The company A receives from the sponsor B cases of SUSARs related to the medicinal product X and originating outside the EEA. What are the reporting responsibilities	In this scenario, the company A is the only source of information in the EEA of the cases of SUSARs. In accordance with EudraLex - Volume 9A, the company A should report, within 15 days from their first knowledge, the cases of SUSARs to the Competent Authorities in the EEA where the medicinal product X is authorised. The cases of SUSARs should also be submitted by the company A to the EudraVigilance Post Authorisation Module (EVPM) within 15 days from their first knowledge. In order to comply with EudraVigilance Business Rules, the ICH E2B(R2) data element A.1.4 *'Type of report'* should be populated with the value (2) 'Report from study' and the ICH E2B(R2) data element A.2.3.3 *'Study type in which the reaction(s)/event(s) were observed'* should be populated with the value (3) 'Other studies'. This is only applicable for those courtesy cases where the company A is not involved in the clinical trial and has no contractual agreement with the sponsor. The company A should also analyse in the corresponding PSUR for the medicinal product X any safety information in relation to the reports of SUSARs, which could impact on the benefit-risk balance of the authorised medicinal product.

Reference number	Questions	Answers
	for the company A regarding the aforementioned cases of SUSARs?	

Part I Chapter 4: Requirements for Expedited Reporting of Individual Case Safety Reports – Requirements by Reporting Source – *Reports from Patients and Other Consumers*

Reference number	Questions	Answers
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 data element ICH E2B(R2) A.1.14 *'Was report medically confirmed if not initially from health care professional'* should be set to 'Yes'. In the data element 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.
ID: 021	EudraLex - 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 an expedited basis. However, sending of reports from patients and other consumers which occurred in Liechtenstein to EudraVigilance is a requirement in EudraLex - 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 EMA 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 EudraLex - Volume 9A. As regards the reporting of these ICSRs, the data element ICH E2B(R2) A.2.1.4 Primary Source *'Qualification'* should be populated with 'Consumer or other non health professional' and 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 'No'.
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 an expedited manner no later than 15 calendar days

Reference number	Questions	Answers
		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 EudraLex - 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.
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. 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.

Part I Chapter 5: Requirements for Reporting in Special Situations – *Reporting Following Suspension or Withdrawal of the Marketing Authorisation for Safety or Commercial Reasons*

Reference number	Questions	Answers
ID: 057	It is stated in Chapter I.5 Section 3 of EudraLex - Volume 9A 'Where a marketing authorisation is withdrawn or revoked, the former Marketing Authorisation Holder is encouraged to continue to report in line with Chapter I.4 to e.g. facilitate review of delayed onset adverse reaction and retrospectively notify cases.' What are the obligations of the former MAH if the medicinal product has never been marketed? Is it acceptable to stop all pharmacovigilance activities after the withdrawal of a medicinal product by the MAH?	According to Article 24 of the Regulation (EC) 726/2004 and of the Article 104 of the Directive 2001/83/EC, pharmacovigilance obligations are related to the holder of the marketing authorisation ("The holder of the marketing authorisation for a medicinal product for human use shall maintain detailed records of all suspected adverse reactions within or outside the Community which are reported to him by a health-care professional"). In case the medicinal product has never been marketed it is considered that the reporting obligations after marketing authorisation withdrawal, as detailed in Chapter I.5 Section 3 of EudraLex - Volume 9A, do not apply.

Part I Chapter 5: Requirements for Reporting in Special Situations – *Reporting of Outcomes of Use of a Medicinal Product During Pregnancy*

Reference number	Questions	Answers
ID: 046	According to the definition of an adverse reaction in EudraLex - Volume 9A, drug exposure during pregnancy (without adverse outcome) is not an adverse reaction. Is it appropriate only to refer to such reports in the PSUR or is it expected that these experiences of drug exposure during pregnancy should be entered in the pharmacovigilance database as single cases?	EudraLex - Volume 9A, Chapter I. 5 section 4 *'Reporting of Outcomes of Use of a Medicinal Product During Pregnancy'*, states that the MAH should follow-up all reports from Healthcare Professionals relating to pregnancies where the foetus may have been exposed to one of his medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure). Individual cases with an abnormal outcome in association with a medicinal product should be reported on an expedited basis. This refers especially to: - Reports of congenital anomalies in the foetus/child, - Reports of foetal death and spontaneous abortion, - Reports of adverse reactions in the neonate that are classified as serious. Other cases, i.e. reports of voluntary termination of pregnancy without information on congenital malformation and reports of pregnancy exposure without outcome data, should not normally be reported on an expedited basis. In certain circumstances, the MAH may be requested to treat any reports of pregnancy exposure as cases requiring expedited reporting, e.g. pregnancy exposure to products contraindicated in pregnancy because of a high teratogenic potential. Not infrequently, pregnant women or Healthcare Professionals will contact either the MAH or Competent Authorities requesting information on the teratogenic potential of a medicinal product and/or experience of use during pregnancy. It is also important to collect information on pregnancies which have a normal outcome and enter the cases in the database. Expedited reports and other reports on outcome of exposure during pregnancy should be included in the PSUR together with aggregated data on the overall exposure and details of normal/abnormal outcomes. Reports from prospective registries should also be included and evaluated in the PSUR.

Part I Chapter 5: Requirements for Reporting in Special Situations – *Reporting from Compassionate/Named-Patient Use*

Reference number	Questions	Answers
ID: 061	What are the reporting rules for suspected adverse reactions related to medicinal products administered in compassionate use programmes?	The reporting requirements of suspected adverse reactions related to medicinal products given in compassionate use programmes, which are not clinical trials, are described in Chapter I.5 Section 7 *Reporting from Compassionate/Name Patient Use* in EudraLex - Volume 9A. The expedited reporting requirements to National Competent Authorities (NCAs) and to EudraVigilance, which are detailed in Chapter I.4 Section 3.1 of EudraLex - Volume 9A, for authorised medicinal products, should also be applied for suspected serious adverse reactions related to medicinal products used in compassionate use programmes. Cases originating in the EEA should be reported electronically to the NCA of the country where the cases originated and to the Rapporteur/Reference Member State by the company responsible for providing the medicinal product. They should not be sent to EudraVigilance as they are transmitted by the NCA of the country where the reaction occurred. Cases originating outside the EEA should be reported electronically to the EudraVigilance Post Authorisation Module (EVPM) and to the NCAs of the countries where the medicinal product is authorised or has active clinical trials or compassionate use programmes. For electronic reporting, the following rules should be followed, in addition to the business rules and validation processes described in the Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (Doc. Ref. EMEA/H/20665/04/Final, Revision 2): - All ICSRs reportable to EudraVigilance, should be sent to EVPM with the message receiver identifier (ICH M2 M.1.5) 'EVHUMAN'. - The ICH E2B(R2) data element A.1.4 *'Type of report'* should be populated with the value (2) 'Report from study'. - The ICH E2B(R2) data element A.2.3.3 *'Study type in which the reaction(s)/event(s) were observed'* should be populated with the value (2) 'Individual patient use'.

Part I Chapter 5: Requirements for Reporting in Special Situations – *Reporting of Lack of Efficacy*

Reference number	Questions	Answers
ID: 052	As stated in EudraLex - Volume 9A Chapter I.5 section 8 'Reporting of Lack of Efficacy', in certain circumstances reports of lack of efficacy should be treated as expedited cases for reporting purposes. In this situation, is it acceptable to submit non-serious expedited cases to the Competent Authorities and/or to EudraVigilance?	When no seriousness criteria are available in reports of lack of efficacy occurring with classes of medicinal products where lack of efficacy should be considered as cases requiring expedited reporting, it is acceptable to submit the cases to the Competent Authorities and/or to EudraVigilance as a non-serious reports. The ICH E2B(R2) data element A.1.5.1 *'Serious'* should contain the value (2) 'No' and none of seriousness criteria in the ICH E2B(R2) data element A.1.5.2 *'Other serious'* should be populated with the value (1) 'YES'.
ID: 053	When reporting cases of lack of efficacy, should the therapeutic indication of the suspected medicinal product be described in the ICH E2B(R2) data element B.2.1 *'Reaction/event in MedDRA terminology'* together with an appropriate MedDRA term to denote lack of efficacy (e.g. drug ineffective)?	Unless aggravation of the medical condition occurs, the indication for which the medicinal product was administered should not be described in the ICH E2B(R2) data element B.2.1 *'Reaction/event in MedDRA terminology'*. If the reporter mentioned a lack of efficacy, this term can be added to the list of the “reactions/events” in MedDRA terminology.

Part I Chapter 5: Requirements for Reporting in Special Situations – *Reporting of Suspected Transmission of Infectious Agents*

Reference number	Questions	Answers
ID: 013	As pointed out in EudraLex - 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) data element 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 one of the following terms for the transmission: - 'Suspected transmission of an infectious agent via a medicinal product' (MedDRA code: 10067593): 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' (MedDRA code: 10067591): 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 be classified as serious in the ICH E2B(R2) data element A.1.5.1 *'Serious'*, and the ICH E2B(R2) data element A.1.5.2. *'Seriousness criteria'* should be set to 'Other medically important condition'.

Part I Chapter 6: Requirements for Periodic Safety Update Reports – Model for a Periodic Safety Update Report (PSUR) – *PSUR section 'Presentation of Individual Case Histories'*

Reference number	Questions	Answers
ID: 038	In Question ID: 012, it is stated that if a report derives from a literature article, which was published in a country where the company does not hold a marketing authorisation, it should not be reported; the company can be excluded as the Marketing Authorisation Holder (MAH). Should these cases still be assessed and listed in the PSUR of the corresponding medicinal product or should they be completely discarded? What is the recommendation for companies where the majority of cases derive from literature?	A Periodic Safety Update Report is intended to provide an update of the worldwide safety experience of a medicinal product to Competent Authorities at defined time points post-authorisation. MAHs are expected to provide succinct summary information together with a critical evaluation of the benefit-risk balance of the medicinal product in the light of new or changing information. In this instance, MAHs should also assess cases or studies published in the literature related to the corresponding active substance(s) of the medicinal product under review in the PSUR even if the company does not have an authorisation in the country where the reaction occurred or where the trial was conducted. Any relevant published safety information which could impact on the benefit-risk balance of the product should be analysed in the PSUR. With regards the expedited reporting of Individual Cases Safety Reports (ICSRs) to the Competent Authorities, the MAH should also consider the country of origin of the report to assume that it is one of its products the report refers to. The recommendation described in Question ID 012 should be followed.

Part I Chapter 7: Company-Sponsored Post-Authorisation Safety Studies – *Ethical Issues*

Reference number	Questions	Answers
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 EudraLex - Volume 9A, sponsors should follow the relevant national legislation in those member states where this exists.

Part III Chapter 5: Preparation of Individual Case Safety Reports and Data Privacy Law – *How to Prepare Individual Case Safety Reports*

Reference number	Questions	Answers
ID: 002	Do the Data Privacy rules for 'Patient name or initials' apply for the electronic submission of ICSRs to EudraVigilance and NCAs?	The guidance provided in EudraLex - 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) data element 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) provided in the data element ICH E2B (R2) B.1.1.1. If the initials are known to the sender but cannot be transmitted due to data privacy requirements, this data element should be populated with 'PRIVACY'. If the initials of the patient are unknown to the sender, this data element 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/foetus report, information concerning the parent'*. The guidance provided in EudraLex - Volume 9A is applicable to: - Submissions to EudraVigilance to both EVHUMAN and EVCTMPROD - 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

Reference number	Questions	Answers
		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 EudraLex - Volume 9A may therefore be applied in every circumstance.
ID: 003	How should the data elements ICH *'Proprietary medicinal product name'* (E2B(R2) B.4.k.2.1) and *'Active substance name(s)'* (ICH E2B(R2) B.4.k.2.2) be populated in the ICSR, when the active substances 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 reports a suspect or interacting branded/proprietary medicinal product name without indicating the active substances of the medicinal product and where the proprietary medicinal product can 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: - Data element *'Proprietary medicinal product name'* (ICH E2B(R2) B.4.k.2.1) should be populated with the proprietary/branded medicinal product name as reported by the primary source. - Data element *'Active substance name(s)'* (ICH E2B(R2) B.4.k.2.2) 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 (data element ICH E2B(R2) A.1.2) or if this is the same, of the country of the primary source, (data element ICH E2B(R2) A.1.1). Where information is available on - The *'Identification of the country where the drug was obtained'* (data element ICH E2B(R2) B.4.k.2.3), - The *'Authorization/application number'* (data element ICH E2B(R2) B.4.k.4.1), - The *'Country of authorization/application'* (data element ICH E2B(R2) B.4.k.4.2) and/or - The *'Batch/lot number'* (data element ICH E2B(R2) B.4.k.3), the composition with regard to the active substance(s) of the proprietary medicinal product should be provided accordingly. In all circumstances, the data element *'Active substance name(s)'* (ICH E2B(R2) B.4.k.2.2) needs to be repeated for each active substance.
ID: 004	How should the data elements *'Proprietary medicinal product name'* (ICH E2B(R2) B.4.k.2.1) and *'Active*	Where the primary source reports a suspect or interacting branded/proprietary medicinal product name without indicating the formulation/presentation of the product and where the proprietary/branded medicinal product can be one of two or more possible

Reference number	Questions	Answers
	substance name(s)' (ICH E2B(R2) B.4.k.2.2) be populated in the ICSR, where the active substances of a branded medicinal product differ depending on the formulation/ presentation marketed?	formulations/presentations in a country, which have a different composition, the ICSR should be populated as follows: - Data element *'Proprietary medicinal product name'* (ICH E2B(R2) B.4.k.2.1) should be populated with the medicinal product name as reported by the primary source. - Data element *'Active substance name(s)'* (ICH E2B(R2) B.4.k.2.2) 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. In all cases, the data element *'Active substance name(s)'* (ICH E2B(R2) B.4.k.2.2) needs to be repeated for each active substance.
ID: 005	How should the data elements ICH *'Proprietary medicinal product name'* (E2B(R2) B.4.k.2.1) and ICH *'Active substance name(s)'* (E2B(R2) B.4.k.2.2) be populated in the ICSR, where the co-medication was reported as e.g. a class of medicinal products?	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 the data element *'Proprietary medicinal product name'* (ICH E2B(R2) B.4.k.2.1) and *'Active substance name(s)'* (ICH E2B(R2) B.4.k.2.2). Instead this information should be provided in the data element *'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information'* (ICH E2B(R2) B.5.1). 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 *'Reactions/Events'* (ICH E2B(R2) B.2) in line with the latest version of the *ICH Endorsed Guide for MedDRA Users, MedDRA Term Selection: Points to Consider.*
ID:011	In spontaneous reports the primary source often provides the diagnoses as well as signs and symptoms related to adverse reactions in the narrative section of the reporting forms. Should	The coding of diagnoses and provisional diagnoses with signs and symptoms in the ICH E2B(R2) data element 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 symptoms of a diagnosis or a provisional diagnosis

Reference number	Questions	Answers
	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?	reported by a primary source/reporter, should be listed and MedDRA coded in the ICH E2B(R2) section B.2 *'Reaction(s)/event(s)'.* It is however considered sufficient to select a term for only the diagnosis or provisional diagnosis and not for the signs 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 data element ICH E2B(R2) B.5.3 *'Sender's diagnosis/syndrome and/or reclassification of the reaction/event'*.
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 data element 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

Reference number	Questions	Answers
		ICH E2B(R2) B.3.1d *'Test result'*: left empty **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
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) has been 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 data element. 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

Reference number	Questions	Answers
		data element ICH E2B(R2) A.2.1.2e *'Reporter state'* is identified by 19 numerical codes (see Appendix H of the Note for Guidance – EudraVigilance Human- Processing of Safety Messages and Individual Case Safety Reports (ICSRs), EMA/H/20665/04/Final Rev. 2, 15 October 2010). 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. - **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 the postcode because it allows classification by regions and cases to be forwarded 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)',*

Reference number	Questions	Answers
		- 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 English. - ICH E2B(R2) B.5.2 *'Reporter's comment',* - ICH E2B(R2) B.5.4 *'Sender's comments'.*
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.

Reference number	Questions	Answers
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 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?	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 EudraLex - 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 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 Periodic Safety Update Report (PSUR) in a dedicated chapter.
ID: 036	Some National Competent Authorities (NCAs) require a translation of the	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'*

Reference number	Questions	Answers
	case narrative in the local language. The current field length of 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, where the limit may be reached with complex legal cases?	exceeds 20,000 characters, the following recommendations should be followed: Create a document in PDF format which contains the case narrative 'overflow'. 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. The PDF file should be sent via e-mail to - EVLIT@ema.europa.eu, for cases originating outside the EEA, or to - The National Competent Authority of the country where the case occurred for cases originating within the EEA. 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 initial report: - *ICSR: ES-ORGABC-23232321 (ICH E2B(R2) data element A.1.10.1 'Worldwide Unique Case Identification Number');* - *File name: ES-ORGABC-23232321.pdf.* Example Follow-up report: - *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*
ID: 049	How to handle the information regarding the country in the ICSR if no ISO 3166 code is assigned yet?	When a code has not yet been allocated by ISO, the ICSR should be coded with the previous ISO country code.
ID: 050	A company A submits an ICSR to company B with information in the	As good case management practice, the original information should be copied by the company B into the ICH E2B(R2) data element B.5.1 *'Case narrative including clinical course, therapeutic*

Reference number	Questions	Answers
	ICH E2B(R2) data element B.5.3 *'Sender's diagnosis/syndrome and/or reclassification of reaction/event'* and/or in the ICH E2B(R2) data element B.5.4 *'Sender's comments'*. How should the company B proceed in order to update the information in these 2 data elements?	*measures, outcome and additional relevant information'* before updating the ICH E2B(R2) data elements B.5.3 and/or B.5.4. The source of the information transferred into the narrative section should also be provided in order to identify it easily in the report.
ID: 056	What are the recommendations for an individual case safety report which has previously been reported, when the Receive date and/or Receipt date were found to be incorrect?	MAHs should make sure that the reported Receive and Receipt dates are precise and correct. If it is found that the submitted Receive date or Receipt date are incorrect, the individual case safety report should be corrected and resubmitted immediately and no later than 15 days.
ID: 058	A company A owns a medicinal product X authorised in only one country within the European Economic Area (EEA) and also in several countries outside the EEA. A patient originating from a non-EEA country and treated with the medicinal product X suffers from a suspected serious adverse drug reaction while visiting an EEA country where the medicinal product X is not authorised. The company A receives the information from the patient's physician when he/she returns to his/her home country outside the EEA.	In this scenario the suspected serious adverse drug reaction occurred in a country within the EEA where the medicinal product X is not authorised, while being authorised in another EEA country. Since the medicinal product X is not authorised in the country of occurrence of the reaction, the company A should report the case directly to EudraVigilance (EudraVigilance Post Authorisation Module) where it will be made accessible to the other Competent Authorities in the EEA where the medicinal product X is authorised.

Reference number	Questions	Answers
	How should this case be handled with respect to reporting to EudraVigilance and to the National Competent Authorities in the EEA?	
ID: 060	A patient receives the medicinal product X in a 21-day chemotherapy cycle. During the first cycle the patient experienced a serious adverse drug reaction (ADR) suspected to be related to the medicinal product X. The ADR recovered before the start of the second cycle. The patient receives the other chemotherapy cycles with the medicinal product X as planned without developing the same ADR. Should the administration of the medicinal product X during the next cycles be considered as a rechallenge?	Because the therapeutic regimen is the same, the subsequent cycles of the medicinal product X administration should be considered as rechallenge. In this example, a follow-up report should be submitted with the negative rechallenge information.

Part III Chapter 6: Nullification of Individual Cases

Reference number	Questions	Answers
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?	The management of duplicates by NCAs is described in EudraLex - Volume 9A chapter II.1 Section 3.3 'Processing Individual Case Safety Reports'. 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 EudraLex - Volume 9A, Chapter III.6 'Nullification of Individual Cases'). Note that in this scenario a nullification of the case is not applicable.
ID: 051	A follow-up information received by a MAH demonstrates that the initially suspected medicinal product was in fact not administered. If the suspected medicinal product which was actually received by the patient is another product of the same MAH, should the reported case be nullified and a new case created?	This case should not be nullified. On receipt of a follow-up information, even though it was confirmed that the patient did not receive the initially suspected drug but another medicinal product, the minimum reporting criteria are still met. The case should be updated with the follow-up information and submitted in accordance with expedited reporting requirements. The medicinal product not administered should be deleted as suspected medicinal product from the report and the correction should be explained in the ICH E2B(R2) data element B.5.1 *'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information'*.

Part III Chapter 7: Handling of Adverse Reactions Reports Published in the Worldwide Literature

Reference number	Questions	Answers
ID: 001	A literature article describes serious adverse reactions 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 EudraLex - 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 data element ICH E2B(R2) 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 data element ICH E2B(R2) 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 **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@ema.europa.eu: UK-ORGABC-0001.pdf **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

Reference number	Questions	Answers
		- ICH E2B(R2) A.2.2 *'Literature reference(s)'*: N Engl J Med. 1997;336:309-15. - No copy of the literature article is 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 is required since the copy was already submitted for case 1.
ID: 007	Will it be possible to send copies 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 EudraLex - Volume 9A 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.
ID: 042	How should MAHs handle literature articles, which present summary data analyses from databases publicly available or which are reporting line listings of patients who experienced ADRs.	These literature articles report adverse drug reactions occurring in a group of patients with a designated medicinal product with the aim of identifying or quantifying a safety hazard related to a medicinal product. They are often linked to pharmacoepidemiological studies and the main objective is to detect/evaluate specific risks that could affect the overall benefit-risk balance of a medicinal product. In this type of literature articles, when safety information could affect the benefit-risk balance of a medicinal product, only one ICSR should be created per literature article. With regards the electronic reporting of the ICSR, in order to comply with the validation processes detailed in the latest version of the EudraVigilance Business Rules (EMA/H/20665/04/Final Rev.2), the following recommendations should be followed: - The ICH E2B(R2) B.1.1 data element *'Patient (name or initials)'*, should be populated with the value 'UNKNOWN'. - A summary of the article, including the number of patients concerned 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'*. - This ICSR should be submitted to the Competent Authorities in line with the reporting rules

Reference number	Questions	Answers
		described in Chapter I.4 of EudraLex - Volume 9A. - The safety findings presented in the article should be discussed in the corresponding PSUR and the publication reference should be provided together with a cross reference to the ICSR.

Part III Chapter 11: Specific Provisions for the Electronic Reporting to EudraVigilance – *Retrospective Electronic Population of EudraVigilance Post-Authorisation Module*

Reference number	Questions	Answers
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 EudraLex - 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 clinical trials and non-interventional studies, all these cases received up to 1 May 2004 should be submitted to the EudraVigilance Post-Authorisation Module (EVPM). 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 EMA should be informed when the retrospective transmission of ICSRs is initiated and what data set will be provided. Furthermore, the EMA should be informed once the retrospective transmission of ICSRs to EVPM has been completed successfully.
ID: 024	What are the rules governing submission of the retrospective transmission of data to the EMA?	The retrospective electronic population of EVPM is covered in Chapter III.11 Section 4 of EudraLex - Volume 9A. As a general principle, the MAH should transmit all cases, which originate from outside the EEA, to EVPM. These cases refer to serious spontaneous reports and serious reports from non-interventional studies. NCAs in the EU should provide reports of all serious spontaneous cases and reports of serious cases from non-interventional studies that originated in their territory. Where no electronic reports or only limited data are available to NCAs in structured format, those NCAs should see to it that the data are entered in EVPM. In practice this means, that NCAs may ask MAHs to transmit retrospectively the cases that originated in their territory, to EVPM on their behalf.
ID: 025	How should the retrospective transmission of ICSRs be performed? - Should the data be in accordance with the ICH E2B(R2) standard?	It is important that retrospectively submitted ICSRs are flagged with the value '*backlog'* in the ICH M2 message header data element M.1.1 *'Message Type'* in order to exclude the retrospective cases from the 15 days expedited compliance monitoring ('*ichicsr'* should NOT be used). The field value is case-sensitive and should be reported in lower case. All messages flagged with the

Reference number	Questions	Answers
	- Is it necessary to complete all data element required for ICH E2B(R2) submission?	value '*backlog'* in the ICH M2 message header data element M.1.1 should be addressed to the message receiver identifier 'EVHUMAN'. The retrospective electronic population of EVPM should follow the applicable ICH standards and guidelines referred to in Chapter III.2 of EudraLex - 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. As with the prospective transmission, not all ICH E2B(R2) data elements should be populated, only those for which structured data are available. However, the cases should contain at least the minimum reporting criteria: a reporter, a patient, a suspect drug and a reaction. A case narrative in English should also be provided in the data element *'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information'* (ICH E2B(R2) B.5.1), in accordance with the guidance in EudraLex - Volume 9A, Chapter III.11 Section 5.
ID: 026	In accordance with EudraLex - 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 which was not able to meet the 1st February 2008 target date for the retrospective transmission of ICSRs as outlined in EudraLex - 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@ema.europa.eu). The concerned organisations should provide - A high level plan as regards the expected date of initiation of the retrospective transmission of ICSRs, - An estimate of the volume of the cases to be transmitted, - The planned date of completion of the retrospective transmission.
ID: 027	How should organisations proceed once they are ready to perform the retrospective transmission of data to the EMA?	As stated in EudraLex - Volume 9A, Chapter III.11 Section 4.1 the sender of retrospectively transmitted ICSRs should perform some initial testing with the EMA, 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@ema.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 EudraLex - Volume 9A, Chapter III.11 Section 4.1. Once the testing has been successfully completed, or if the transmission is being performed via the

Reference number	Questions	Answers
		EVWEB, the organisation should contact Tom Paternoster (tom.paternoster@ema.europa.eu), in order to inform the EMA about - The date of the initiation of the retrospective transmission of ICSRs, - An estimate of the volume of the cases to be transmitted, - The planned date of completion of the retrospective transmission.
ID: 028	What are the reporting criteria to retrospectively transmit ICSRs 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 retrospectively all reports of serious spontaneous cases and all reports of serious cases from non-interventional studies originating in those countries for the period of 1 January 1995 until the date of accession to the EU. For example, for those Member States, which joined the EU on the 1st May 2004, the MAHs should retrospectively transmit for those countries the ICSRs 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, the MAHs should retrospectively transmit for these countries the ICSRs covering the period from 1st January 1995 to 31 December 2006.

Part III Chapter 11: Specific Provisions for the Electronic Reporting to EudraVigilance – *Handling of Languages*

Reference number	Questions	Answers
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 – Chapter 1 – 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. **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.

Part III Chapter 11: Specific Provisions for the Electronic Reporting to EudraVigilance – *Population of the EudraVigilance Medicinal Product Dictionary*

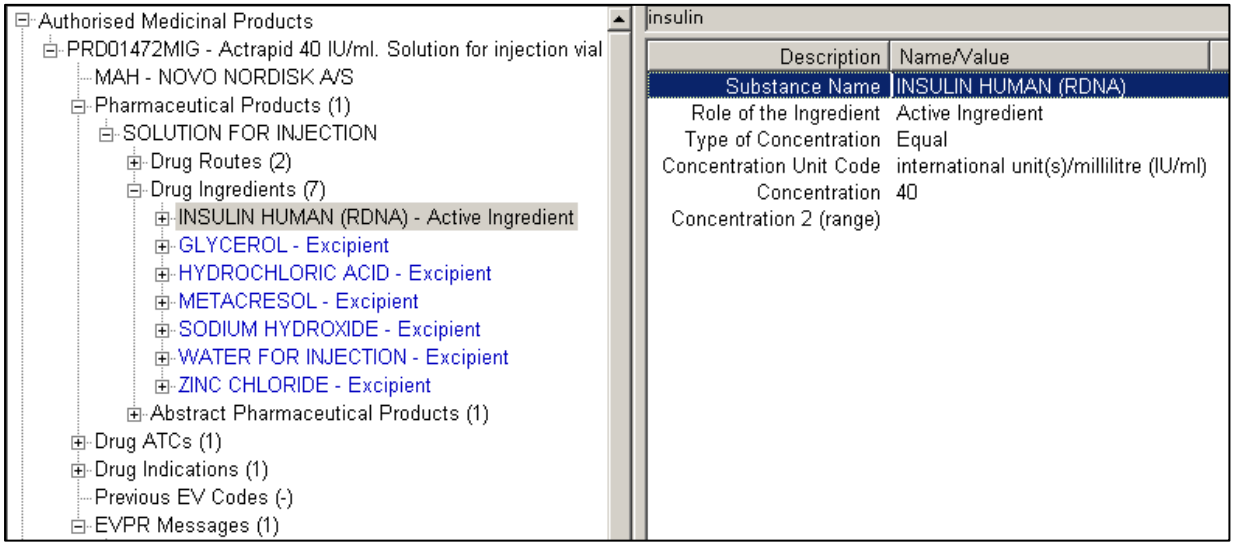
Reference number	Questions	Answers
ID: 015	What needs to be taken into account in populating the EVMPD as regards vaccines? Which EVMPD field should be populated?	In addition to the recommendations regarding the population of the EudraVigilance Medicinal Product Dictionary (EVMPD) detailed in the *'EVMPD 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. iii. 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. iv. The EVMPD contains a look-up of common names as described in the European Pharmacopoeia, which is systematically updated by the EMA. v. 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 EMA.

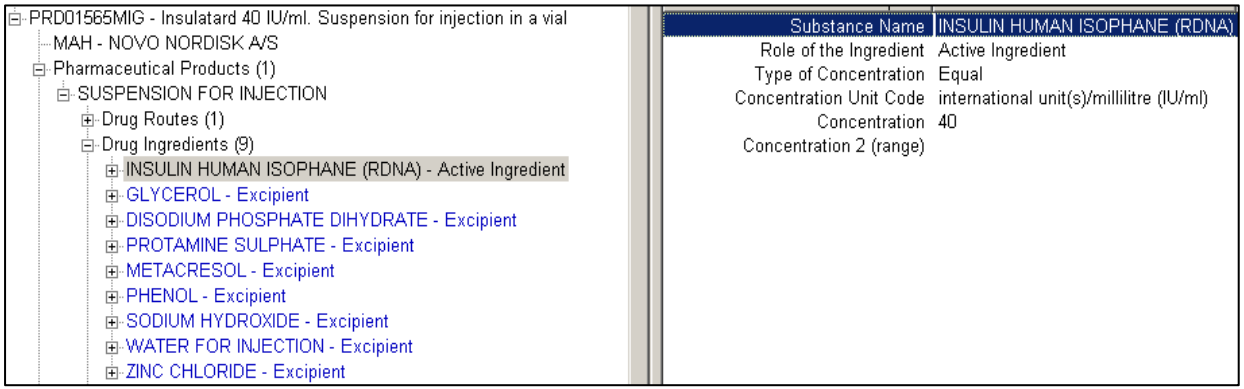
Reference number	Questions	Answers
		iv. If a vaccine antigen cannot be found in the EVMPD look-up, the MAH/sponsor of clinical trials should contact the EudraVigilance Helpdesk to obtain guidance on how the antigen should be presented. - The vaccines adjuvant(s)/adsorbant should be entered in the EVMPD 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+). For a full list of excipients, see section 6.1.* ** produced from recombinant strain of the yeast Saccharomyces cerevisiae (strain 2150-2-3).* - *SmPC Section 6.1: 'LIST OF EXCIPIENTS'*

Reference number	Questions	Answers
		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 Example EVMPD presentation for HBVAXPRO: 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

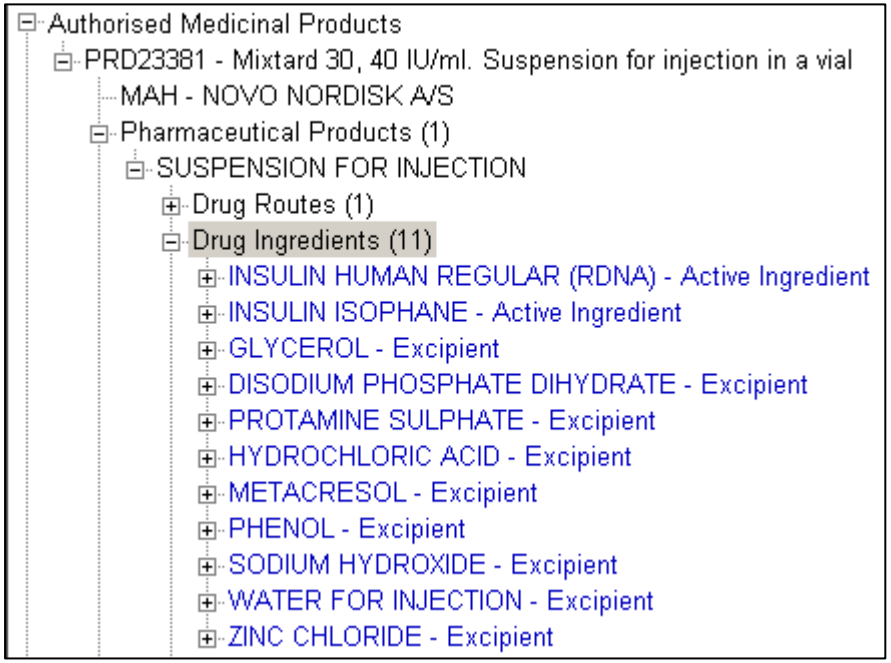
Reference number	Questions	Answers
ID: 016	What needs to be taken into account in populating the EVMPD as regards insulins? Which EVMPD field should be populated?	In addition to the recommendations regarding the population of the EudraVigilance Medicinal Product Dictionary (EVMPD) detailed in the *'EVMPD training material'*, the following should be taken into account for insulins: **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 International Non-Proprietary Name (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 EMA in collaboration with the CHMP Biological Working Party. 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. vi. The active ingredient can refer to *'Insulin Substance(s)'*, *'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. **d.** 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

Reference number	Questions	Answers
		molecule can be described by the following elements: i. Insulin Type: provides information on the final amino acid sequence (i.e. bovine, porcine or human sequence). ii. Insulin Analogue: provides information whether the insulin has been modified in its amino acid sequence through recombinant technologies. iii. Insulin Class: provides information on the preparation process (e.g. Recombinant, Semi-synthetic, Non-synthetic). iv. Example: Insulin Human rDNA. - *'Insulin Formulation'* referring to insulins that have been combined with other molecules or insulins can be described by the following elements: i. Physical State: provides information on the physical state of the insulin formulation following completion of the preparation process. ii. Complexing: provides information on the particles or molecules that have been combined with the insulin (e.g. Insulin Zinc Crystalline). iii. 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). iv. Duration of action: provides information on how long the insulin is lowering the blood glucose. v. 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 (…) For a full list of excipients, see section 6.1.* - *SmPC Section 6.1: 'LIST OF EXCIPIENTS'*

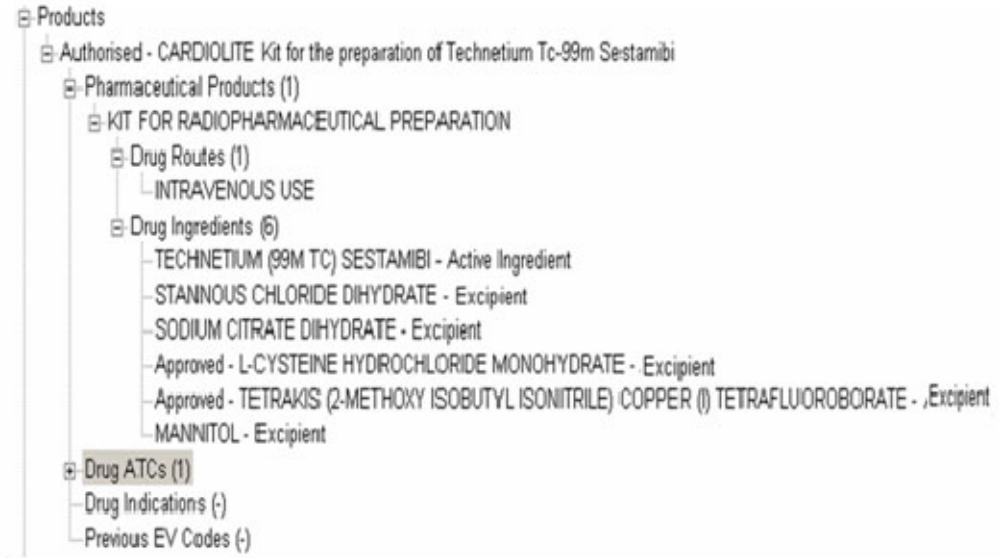
Reference number	Questions	Answers
		Zinc chloride, *Glycerol,* *Metacresol,* *Sodium hydroxide or/and hydrochloric acid (for pH adjustment),* *Water for injections.* Example: EVMPD presentation for ACTRAPID  **Example 2: SmPC INSULATARD** (Insulin Medicinal Product containing an Insulin Formulation) - *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).*

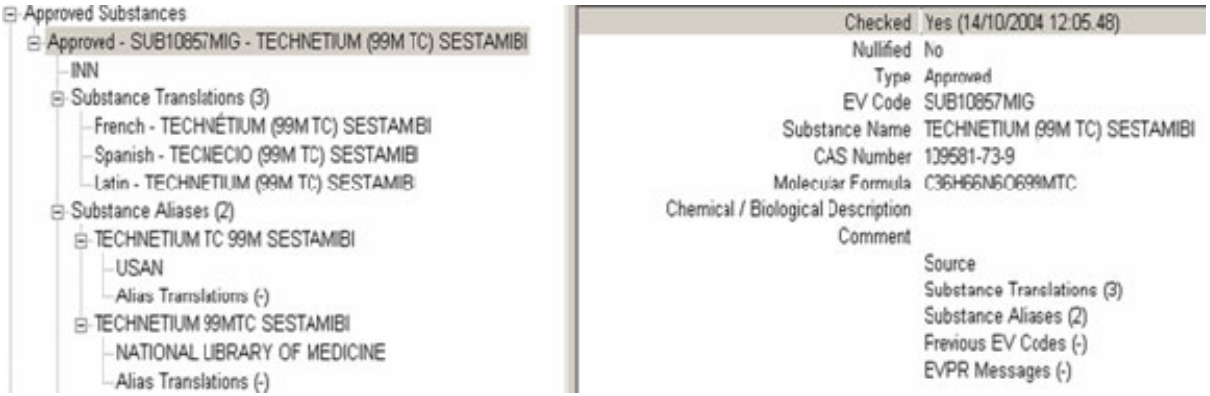
Reference number	Questions	Answers
		1 ml contains 40 IU of insulin human. (…) Insulatard is a suspension of isophane (NPH) insulin. For excipients, see Section 6.1 List of excipients. - *SmPC Section 6.1: 'LIST OF EXCIPIENTS'* *Zinc chloride,* *Glycerol,* *Metacresol,* *Phenol,* *Disodium phosphate dihydrate,* *Sodium hydroxide or/and hydrochloric acid (for pH adjustment),* *Protamine sulphate,* *Water for injections.* <u>Example: EVMPD presentation for INSULATARD</u>  **<u>Example 3: SmPC MIXTARD</u>** (Insulin Medicinal Product containing combination of insulin substance and/or formulation) - *SmPC Section 1: 'NAME OF THE MEDICINAL PRODUCT'* *Mixtard 30, 40 IU/ml,*

Reference number	Questions	Answers
		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,* *Glycerol,* *Metacresol,* *Phenol,* *Disodium phosphate dihydrate,* *Sodium hydroxide or/and hydrochloric acid (for pH adjustment),* *Protamine sulphate,* *Water for injections.*

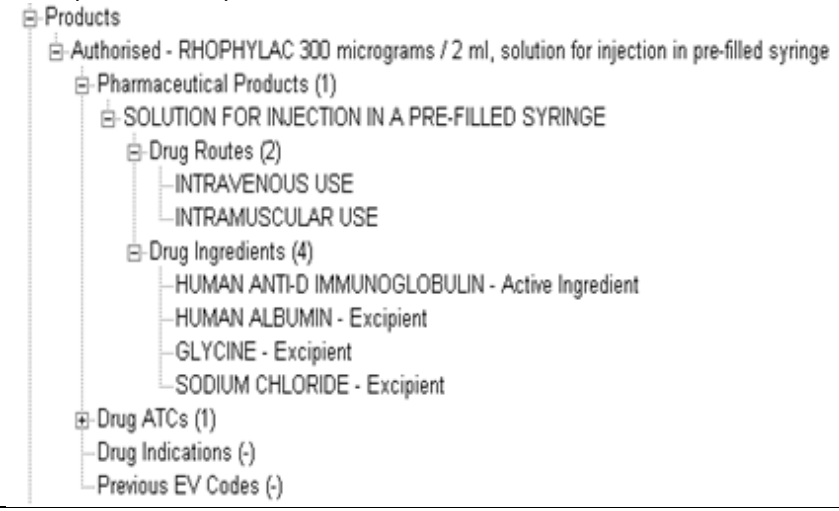
Reference number	Questions	Answers
		Example: EVMPD presentation for MIXTARD 
ID: 017	What needs to be taken into account in populating the EVMPD as regards radioactive compounds? Which EVMPD field should be populated?	In addition to the recommendations regarding the population of the EudraVigilance Medicinal Product Dictionary (EVMPD) detailed in the *'EVMPD training material'*, specific topics related to radioactive compounds only should be taken into consideration 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'*.

Reference number	Questions	Answers
		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. 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 described in European Pharmacopoeia, which is systematically updated by the EMA. 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®** - *Section 1. NAME OF THE MEDICINAL PRODUCT* *CARDIOLITE®, Kit for the preparation of Technetium Tc-99m Sestamibi.*

Reference number	Questions	Answers
		- *Section 2. QUALITATIVE AND QUANTITATIVE COMPOSITION* *1 vial contains* *Active ingredients :* *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.* <u>Example: EVMPD presentation for CARDIOLITE®</u> 

Reference number	Questions	Answers
		Example: EVMPD presentation for Technetium (99mTc) Sestamibi 
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 recommendations regarding the population of the EudraVigilance Medicinal Product Dictionary (EVMPD) detailed in the *'EVMPD training material'*, specific topics related to immunoglobulins only should be taken into consideration 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 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

Reference number	Questions	Answers
		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 EMA in collaboration with the CHMP Biological Working Party. vii. 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 field should be populated. **Example: SmPC RHOPHYLAC®** - *Section 1. NAME OF THE MEDICINAL PRODUCT* *RHOPHYLAC® 300 micrograms / 2 ml, solution for injection in pre-filled syringe.*

Reference number	Questions	Answers
		- *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.* <u>Example: EVMPD presentation for RHOPHYLAC®</u> 

Reference number	Questions	Answers
		Example: EVMPD entry for Human Anti-D Immunoglobulin