



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

23 November 2018  
Information Management Division  
EMA/679813/2018

## The launch of the new EudraVigilance System

### Questions and Answers (Q&A) from stakeholders

Version 1.7

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## Glossary

| <b>Acronym</b> | <b>Definition</b>   |
|----------------|---|
| ACK / NACK     | Acknowledgment / Negative Acknowledgment  |
| ARISg          | Aris Global (web-based adverse event software )   |
| ATU            | Authorisation temporaire d'utilisation  |
| BFC            | Backward and Forward conversion   |
| CRO            | Contract Research Organisation  |
| DEC            | Drug event combination  |
| EDI            | Electronic Data Interchange   |
| EEA            | European Economic Area  |
| EMA            | European Medicines Agency   |
| EPITT          | European Pharmacovigilance Issues Tracking Tool   |
| eRMRs          | Electronic Reaction Monitoring Reports  |
| EU             | European Union  |
| EUQPPV         | European Qualified Person Responsible for Pharmacovigilance                                 |
| EVCTM          | EudraVigilance Clinical trial Module  |
| EVDAS          | EudraVigilance data analysis system   |
| EV-EWG         | EudraVigilance Expert Working Group   |
| EVPM           | EudraVigilance Post-Authorisation Module  |
| EVPOST         | EudraVigilance post function  |
| EVWEB          | EudraVigilance web reporting application  |
| FU             | Follow up   |
| GVP            | Good pharmacovigilance practice   |
| HQ             | Headquarter   |
| ICH            | International Conference on Harmonisation   |
| ICSR           | Individual case safety report   |
| IG             | Implementation Guide  |
| ISO IDMP       | International Organization for Standardization for the identification of medicinal products |
| MAHs           | Marketing authorisation holders   |
| MedDRA         | Medical Dictionary for Regulatory Activities  |
| MLM            | Medical literature monitoring   |
| NCA            | National competent authorities  |
| NPhVD          | The National Pharmacovigilance Database   |
| PBRER          | Periodic benefit-risk evaluation report   |
| PRAC           | Pharmacovigilance Risk Assessment Committee   |
| PSMF           | Pharmacovigilance system master files   |

| <b>Acronym</b> | <b>Definition</b>                                    |
|----------------|--|
| PSUR           | Periodic Safety Update Report                        |
| PSUR DLP       | PSUR Data lock point                                 |
| QPPV           | Qualified Person Responsible for Pharmacovigilance   |
| ROR            | Reporting Odds Ratio                                 |
| RPhV           | Responsible of Pharmacovigilance                     |
| SD             | Signal detection                                     |
| SDR            | Signal of disproportionate reporting                 |
| SMQs           | Standardized MedDRA Query                            |
| WW ID          | World Wide ID  |
| XCOMP          | EudraVigilance test environment                      |
| XEVMPD         | Extended EudraVigilance Medicinal Product Dictionary |
| XML            | Extensible Mark-up Language                          |

## **Introduction**

This document addresses questions received from stakeholders as a part of the launch of the new EudraVigilance System, which went live on 22 November 2017.

The document summarises questions received through the Agency's service desk and as part of the EudraVigilance technical and pharmacovigilance support webinars organised by the EMA.

The document is regularly updated and should be consulted as a first reference before contacting the Agency's service desk.

## 1. EudraVigilance organisation and user registration

| Ref.                    | Question   | Answer  |
|-------------------------|--|---|
| 1.1<br><b>(Updated)</b> | Can an individual only be registered under one Organisation Identifier (ID)?   | In accordance with the established process, a user can be registered with several organisations, which are characterised by their OMS org ID. The user can access their EV restricted area for production using their unique single sign on that can be retrieved from <a href="#">EMA Account Platform</a> . For XCOMP, they will receive a different user name and password for each organisation and will obtain access to data as determined by the EU Qualified Person Responsible for Pharmacovigilance (QPPV) (or the appointed deputy) of each organisation, as applicable. |
| 1.2                     | Can a user be registered both, at headquarter (HQ) level and at affiliate level of the same organisation?  | A user can be registered both at headquarter level and at one or more affiliates of this headquarter.   |
| 1.3                     | If a user from a third party is given a user account linked to the headquarters of the organisation, will the third party user have access to all ICSRs of the organisation? | Yes. Taking into account that the "Owner HQ Identifier" is used to determine the access for ICSRs by marketing authorisation holders (MAHs), a user registered at headquarters level will have access to ICSRs for all active substances for which the organisation at headquarter level holds marketing authorisations in the EEA.   |
| 1.4<br><b>(Updated)</b> | Is the registration process different for access to XEVMPD and where is the online application for updating the XEVMPD data?   | <p>The XEVMPD is no longer part of the new EVWEB as the current XEVMPD will be replaced at the time of the ISO IDMP implementation. For details refer to the EMA webpage on 'Implementation of the ISO IDMP standards').</p> <p>The XEVMPD will be maintained until that time and the URL for access is:<br/><a href="https://eudravigilance.ema.europa.eu/X/?6">https://eudravigilance.ema.europa.eu/X/?6</a></p> <p>To use the XEVMPD, new users should follow the established <a href="#">EV registration process</a>.</p>   |

| Ref. | Question  | Answer   |
|------|---|--|
| 1.5  | Is there a limit to the number of users who can be registered with EVWEB to ICSR reports/download ICSRs?  | EMA has not defined a maximum number of users per organisation that can register with EVWEB. It is recognised that the number of users depends on the size of an organisation and how each organisation defines its business processes in relation to the interaction with EudraVigilance. Performance and scalability testing has been performed by the Agency based on concurrent users of the system. EMA is continuously monitoring the usage of the system, which is based on a scalable design.  |
| 1.6  | What is the Agency's position on MAH personnel who reside outside of the EEA accessing data from EudraVigilance for the purposes of signal evaluation/signal detection activities? Are there any "data privacy" constraints that have been considered here? | <p>The EudraVigilance database is made accessible to the EU QPPV as the regulatory representative of the MAH. The QPPV, as a representative of the MAH, shall be established in the EU territory, and therefore it must be subject to EU data protection law.</p> <p>This implies that it is the MAH, as a data controller under the applicable legislation that should ensure that the access to the data via its organisation is in compliance with EU data protection law, i.e. that the transfer of data within the MAH is in line with the applicable rules. There are therefore no geographic restrictions from the EMA perspective to non-EEA users as the responsibility for these users rests solely with the authorised representative of the MAH.</p> |

| Ref.                    | Question   | Answer   |
|-------------------------|--|--|
| 1.7                     | <p>What is the difference in the administrative and scientific profile of EVDAS users?</p> <p>Can an MAH have five registered users for each profile?</p> <p>What is the rationale for the limitation in users?</p> <p>We'd like to suggest considering that the number of registrations should instead be proportionate to the number of marketing authorisations that a company holds in the EU/EEA.</p> | <p>The number of EVDAS users for each MAH has been defined with five users for both the administrator and scientific profile. The EVDAS scientific profile allows users generating electronic Reaction Monitoring Reports (eRMRs), line listings and downloading individual cases. The EVDAS administrator role allows generating eRMRs and line listings but excludes the download of individual cases e.g. an administrator can generate eRMRs and line listings for all substances for which an MAH holds a marketing authorisation in the EEA.</p> <p>Users with an administrator profile can distribute the eRMRs and associated line listings to the signal management teams within the organisation. The signal management experts can access the individual cases of interest via EVWEB.</p> <p>EMA has defined a maximum number of users per organisation to ensure optimal performance of EVDAS. It is recognised that the number of users is linked to the size of an organisation and how each organisation defines its business processes in relation to the interaction with EudraVigilance. Performance and scalability testing has been carried out by the Agency based on concurrent users of the system. EMA is continuously monitoring the usage of the system, which is based on a scalable design and taking into account initial experience gained, may revisit the number of EVDAS users for MAHs with a large product portfolio.</p> |
| 1.8                     | <p>Can the QPPV access be delegated? Given there are complex arrangements for medicinal products licenced across multiple MAHs, can the Company A QPPV access be delegated to someone in Company B?</p>  | <p>From a registration perspective the EU QPPV (company A) can delegate the functions related to EudraVigilance registration to a trusted deputy (e.g. a trusted deputy of company B). The trusted deputy can then perform the registration of new users, affiliates and any other changes on behalf of the EU QPPV (company A).</p> <p>The overall responsibility for EudraVigilance access and user registration remains with the EU QPPV (company A).</p>   |
| 1.9<br><b>(Updated)</b> | <p>How do I register users for EVDAS and EudraVigilance with EVWEB so they can access individual cases from the individual case line listing?</p>  | <p>Please see question 1.16. To Register in EVDAS and EVWEB, users will need to request the relevant role via manage my access tab in the EMA Account Portal. Registering a user with an EVDAS scientific profile does not add the EVWEB profile to create/send ICSRs. The EVWEB profile to create/send ICSRs can be chosen in addition.</p>   |

| Ref.                     | Question   | Answer  |
|--------------------------|--|---|
| 1.10<br><b>(Updated)</b> | Which username and password have to be used to enter into EVDAS for MAH? The same as to enter into Eudralink or to EMA Service Desk? | To access EVDAS (via the BI tool) users need to use the same password as for their EV Human Production credentials. |
| 1.11<br><b>(Updated)</b> | How long does it take from EVDAS access being requested by an MAH user to the EMA providing access?                                  | The process requires the QPPV or trusted deputy to approve access; this is no longer dependant on EMA.              |

| Ref.                                | Question  | Answer  |
|-------------------------------------|---|---|
| <p>1.12</p> <p><b>(Updated)</b></p> | <p>With the release of EVDAS functionality, we would like to ask about registration for service providers / CROs.</p> <p>May MAHs outsource their signal detection activities; therefore it is important that these service providers / CROs have adequate access to the EVDAS system.</p> <p>Will a service provider be able to gain access to the system independently to perform signal screening for multiple MAHs?</p> <p>If this is not possible and an MAH would like to register a service provider/CRO to perform the screening on their behalf, how can this be done? For example when MAHs do not wish to register a CRO user at headquarters level, or require more than 5 users?</p> | <p>The obligation related to the monitoring of EudraVigilance is placed on the marketing authorisation holder (MAHs) as follows: "MAHs shall monitor the data available in the EudraVigilance database to the extent that they have access to that database". [Commission Implementing Regulation 520/2012 Art 18(2)]</p> <p>The legislation does not foresee access to EudraVigilance data by service providers or CROs.</p> <p>However, CROs and IT vendors may be registered by an MAH, applicant, commercial or non-commercial sponsor as a third party service provider acting on behalf of the organisation by providing services related to EudraVigilance. These entities will be registered as Virtual affiliates of the MAH.</p> <p>It is for the MAH/sponsor to define how they organise the reporting of suspected adverse reactions and the monitoring of the data available in the EudraVigilance database. EVDAS registrations are to be approved by the EU QPPV or the appointed deputy and access to EVDAS data for the purpose of signal management is only granted at headquarter level.</p> |

| Ref. | Question  | Answer  |
|------|---|---|
| 1.13 | <p>Regarding the role of the EUQPPV:</p> <p>Is it possible for an affiliate to have its own EUQPPV, and in this case, does the QPPV endorse all the responsibilities for the affiliate pharmacovigilance system, or is the EU QPPV of the headquarters still responsible?</p> | <p>In accordance with Articles 8 and 104 of the Directive 2001/83/EC, a single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the pharmacovigilance system master file. Each pharmacovigilance system can have only one QPPV. A QPPV may be employed by more than one marketing authorisation holder, for a shared or for separate pharmacovigilance systems or may fulfil the role of QPPV for more than one pharmacovigilance system of the same marketing authorisation holder, provided that the QPPV is able to fulfil all obligations.</p> <p>Please note that the Article 104(4) of Directive 2001/83/EC gives the possibility for EU Member States to request the nomination of a contact person for pharmacovigilance issues at national level reporting to the qualified person responsible for pharmacovigilance activities (QPPV). Reporting in this context relates to pharmacovigilance tasks and responsibilities and not necessarily to line management. A contact person at national level may also be nominated as the QPPV.</p> <p>This provision is intended to be implemented in the national laws of the EU Member States which decide to use this possibility and, as such, to be applied, enforced and interpreted by the national competent authorities of these EU Member States.</p> <p>The Information relating to the responsibilities of the contact person for pharmacovigilance issues where such a person has been nominated at national level shall be included in the PSMF [IR Art 2(1)] (see Module II). Contact points shall be established [IR Art 14(1)], in particular to facilitate interaction between competent authorities, marketing authorisation holders and persons reporting information on the risks of medicinal products as regards patients' or public health.</p> <p>Please find following the link regarding the "<a href="#">Information on the Member States requirement for the nomination of a pharmacovigilance (PhV) contact person at national level</a>".</p> <p>The information in the document was compiled on the basis of feedback provided by the Pharmacovigilance Inspectors Working Group in response to a dedicated survey. EMA has only reproduced the feedback provided by the national competent authorities of the EU Member States. The document is not intended as a legal advice or detailed guidance on how to comply with the national laws of the EU Member States implementing Article 104(4) of Directive 2001/83/EC.</p> |

| Ref.                     | Question   | Answer  |
|--------------------------|--|---|
| 1.14<br><b>(Updated)</b> | What are the registration and testing requirements for a new vendor who has never reported to EudraVigilance before and who will report ICSRs via EVWEB after Nov 22nd?  | <p>The EudraVigilance registration and testing process are published on the EMA website, please refer to the section IT vendors and third party service providers for specific information for vendor registration and testing</p> <ul style="list-style-type: none"> <li>• <a href="#">EudraVigilance: How to register</a></li> <li>• <a href="#">EudraVigilance: Testing process</a></li> </ul>   |
| 1.15<br><b>(Updated)</b> | When registering a virtual affiliate under the headquarter-account of an MAH, in which scenarios is an additional Responsible Person for EV different from the headquarter-QPPV needed? The virtual affiliate is a third party service provider who is going to perform safety reporting for a clinical trial. | <p>The EU QPPV or responsible Person for EudraVigilance (RPEV) at headquarter level appoints users and designates their permissions.</p> <p>There is no obligation for a sponsor to appoint a RPEV at virtual affiliate level.</p> <p>If the affiliate is an MAH, a local QPPV should be registered for this affiliate.</p> <p>If the local QPPV is the same person as the EU QPPV at headquarter level, this person does not need to be registered under the MAH affiliate. Virtual affiliates do not have RPEV, as the EU QPPV is the responsible for this affiliate.</p> |

| Ref.           | Question  | Answer   |
|----------------|---|--|
| 1.16           | Will employees having access to EVDAS also have access to EVWEB? Or for CIOMs it will be visible only through a link in eRMR?   | <p>Registered users are able to retrieve data according to the registration profile. There are 2 profiles available for registration:</p> <ul style="list-style-type: none"> <li>• EVDAS scientific profile: access EVDAS and related reports, including electronic reaction monitoring reports (e-RMRs), active substance groupings, line listings and Individual Case Safety Report forms. <ul style="list-style-type: none"> <li>– <b>Access to the ICSR form is directly from the EVDAS line listing but the system will connect to EVWEB and therefore users with a scientific profile in EVDAS will need to have EVWEB access.</b></li> </ul> </li> <li>• EVDAS administrative profile: access to e-RMRs and line listings available to signal management teams within their organisation.</li> </ul> <p>Details and instructions on the EVDAS registration are provided on the <a href="#">EV website</a></p>   |
| 1.17 (Updated) | <p>Regarding XEVMPD is it possible to have several QPPVs registered for the same account (i.e. if a QPPV is registered for an affiliate, can the QPPV of the affiliate be selected while creating a new product in XEVMPD instead of the EUQPPV of the headquarter)?</p> <p>After the creation of an affiliate, will the affiliate have its own account for the XEVMPD or will the affiliate share the same account as the headquarter?</p> | <p>There can be local QPPVs (request the additional QPPV role in EMA Account Management portal) registered under the same EV organisation at affiliate level. The EU QPPV needs to be registered at headquarter level of an organisation. Based on the national requirements in Member States, a local QPPV may need to be appointed by the MAH. This information can be reflected at affiliate level as applicable. When a QPPV is registered as part of the EudraVigilance process, a QPPV code for that QPPV is generated within the XEVMPD. This code can then be selected when submitting product information to the XEVMPD. Whether the QPPV is under the HQ profile or under an affiliate of the same HQ, their QPPV code can be used in medicinal products.</p> <p>There is no notion of an "XEVMPD account". Normally all QPPV codes generated within an organisation group (i.e. under the headquarter profile and its affiliates) can be used in medicinal products across the group.</p> |

| Ref.                     | Question  | Answer  |
|--------------------------|---|---|
| 1.18<br><b>(Updated)</b> | When registering a sponsor in EudraVigilance, some information must be filled in by the EU QPPV/RP once they have access to their Restricted area. One of the items to be provided is the "MedDRA license number": is this the sponsor's or the third party service provider's? | Organisations registering in EudraVigilance are required to purchase their own MedDRA licence. Although a Third Party Service Provider must also have a MedDRA licence, for the purposes of EV registration it is the registering organisation that should provide their MedDRA licence number. More information on this topic can be found in the <a href="#">Q&amp;A section of the MedDRA MSSO website</a> (select option 'MedDRA subscription').  |
| 1.19                     | Following the registration in EudraVigilance, could you specify what is the difference between "affiliate" and "virtual affiliate" regarding the information that should be provided?   | The term 'virtual affiliate' refers to an affiliated profile under a HQ organisation, which is registered for the purposes of registering a Third Party Service Provider, or for using a different transmission mode to that of the HQ profile. A 'virtual affiliate' is not an actual entity of the HQ organisation. An actual affiliate is an organisation that belongs to the HQ by way of ownership or any other legal arrangement (e.g. HQ is based in Germany and it registers its affiliates based in Italy and France). |
| 1.20<br><b>(Updated)</b> | Where/how can the QPPV request Level 2B access for users?   | Level 2B access can be granted by the registered QPPV or responsible for EudraVigilance.<br>Users need to access their EMA Account Management portal, select the "Manage my access" tab and request the L2B role.<br>EU QPPVs/TDs and RPs can approve this role via the EMA Account Portal, in the "Approvals" tab.<br><a href="#">"EudraVigilance: Registration User Management"</a>   |

## 2. Use of EVWEB and the ICSR download manager

| Ref. | Question   | Answer  |
|------|--|---|
| 2.1  | <p>The ICSR download eLearning video states that there is no need to specify the active substance or medicinal product name in the filter as the download includes all ICSRs for medicinal products registered by the MAH in the EVXMPD.</p> <p>Based on this, is it correct that MAHs won't be getting cases where another MAHs medicinal product name is reported.</p> | <p>The download function is based on the EudraVigilance Access Policy L2A. <i>Access is based on the active substance</i> for medicinal products, for which an MAH holds a marketing authorisation. Therefore the download algorithm does not exclude ICSRs where the medicinal product of another MAH is reported in the ICSR.</p> <p>Downloaded ICSRs contain information on the medicinal product as reported by the primary source, which allow an MAH to determine ownership of the medicinal product.</p> <p>Please refer to slide 62 onwards of the <a href="#">EudraVigilance Access Policy eLearning material</a> and 36:55 of the <a href="#">eLearning video on EudraVigilance Access Policy</a></p> |
| 2.2  | <p>Are only valid ICSRs available for download?</p>  | <p>The EudraVigilance Access Policy states that ICSRs classified as 'Error Reports' are excluded from access as they refer to incomplete or erroneous reports. If an ICSR is classified as 'Error Report', the sender is required to correct the ICSR and retransmit it before it can be further processed in EudraVigilance.</p> <p>Please refer to slide 22 of the <a href="#">EudraVigilance Access Policy presentation</a> and 10:35 of the <a href="#">eLearning video on EudraVigilance Access Policy</a></p>   |

| Ref.                    | Question  | Answer   |
|-------------------------|---|--|
| 2.3<br><b>(Updated)</b> | <p>What clock start date should an MAH use (e.g. for onward sending outside the EEA)?</p> <p>Is this defined by the EMA or left to MAHs to decide i.e. based on download date as per MLM?</p> <p>In addition, how can I see in a case downloaded via EVWEB ICSR download functionality when this case was first available for download?</p> | <p>The pharmacovigilance legislation does not define a "day zero" for ICSRs accessed via EudraVigilance by MAHs.</p> <p>For ICSRs to be included in PSURs, the MAH should define what the cut-off date is for ICSRs downloaded from EVWEB as part of the PSUR data lock point.</p> <p>For reporting obligations outside the EEA, MAHs need to consult with the respective regulatory authorities and their requirements.</p> <p>For MLM ICSRs, the following is agreed: The clock starts (day zero) with awareness of a publication containing the minimum information for reporting. In practice this means that for records of confirmed ICSRs, the clock starts for the MLM Service at the time of performing the search; whereas for marketing authorisation holders the clock starts when the information on which substances are suspected to have caused a reaction is made available to marketing authorisation holders. This information is first made available when the ICSR is transmitted to EudraVigilance; therefore the date of transmission of an ICSR by the MLM Service to EudraVigilance is day zero for marketing authorisation holders in the EEA. MAHs should ensure that they download cases regularly.</p> <p>Were an MAH to adopt the same principles for L2A downloads as they would for the MLM Service downloads, then, given the advice in question 2.125 to set the date range as 3 days ago, the date of downloading would be used as the day zero. This information is in the zip file that is downloaded, in the "Date modified" column.</p> |
| 2.4                     | Do ICSR messages retrieved from EVWEB contain local language content?   | ICSRs are made available in the language as they were reported to EudraVigilance. If for example an NCA submits ICSRs that contain local language in free text data elements, access to these data elements is provided in accordance with the EudraVigilance Access Policy (revision 3). For language requirements, refer to Article 28(4) of the Commission Implementing Regulation (EU) 520/2012.   |

| Ref. | Question  | Answer  |
|------|---|---|
| 2.5  | Please confirm what dates are used to perform the export of ICSR messages. Are these the dates received by the EudraVigilance (EV) system or the E2B data element "Receive date", or the gateway "Transmission date"? | <p>The ICSR download functionality uses the date that the ICSRs suspect and interacting drugs have been classified against the data held in XEVMPD/Art.57 database. Classification is either performed automatically in the EudraVigilance Database Management System (EDBMS) or, if not automatically classified (e.g. due to data quality issues in the reported ICSR), is performed at a later stage through the manual classification process.</p> <p>The MAH access to data in accordance with the EudraVigilance Access Policy (revision 3), i.e. levels L2A/L2B depends on the completion of the classification process. As the linkage of ICSRs to XEVMPD/Art.57 data can only occur through the classification process (automatic or manual), the date that the suspect or interacting drug(s) have been classified against the data held in XEVMPD/Art.57 database is used by the ICSR download tool rather than the official receipt date of the ICSR.</p> |
| 2.6  | Is a user's login ID connected to an Organisation ID to obtain a list of "Active Substances" associated with that Organisation's ID?  | <p>A user's login ID is linked to the related organisation, for which the user is registered. The user's organisation ID is also linked to the XEVMPD/Art.57 data, based on the data element "Owner HQ Identifier". The XEVMPD/Art.57 data associated through this linkage determine which ICSRs can be accessed by the MAH in EudraVigilance.</p> <p>Only MAH user's registered at headquarter level are be able to make L2 access requests.</p>   |
| 2.7  | Large organisations have many active substances registered in the XEVMPD/Art.57 database. Is there a way to distinguish between serious and non-serious ICSRs from the file names or using query criteria?            | <p>The ICSR download tool now includes a filter that allows organisations to select ICSRs that are "Serious", "Non-serious" or both.</p>  |

| Ref. | Question   | Answer   |
|------|--|--|
| 2.8  | How can an MAH determine if an E2B(R3) ICSR is serious before loading it into the local database?    | <p>The following two options might be considered:</p> <p>Organisations can either use the ICSR download filter to select just serious ICSRs, or alternatively you can use the following XPATH statement to determine if an ICSR in E2B(R3) format is serious. If the resulting value of the count is greater than 0 it means that at least one reaction has one of the seriousness criteria marked as "Yes".</p> <pre>count(/MCCI_IN200100UV01/PORR_IN049016UV/controlActProcess/subject/investigationEvent/component/adverseEventAssessment/subject1/primaryRole/subjectOf2/observation/outboundRelationship2/observation[code[@code='34' or @code='21' or @code='26' or @code='33' or @code='35' or @code='12'][@codeSystem="2.16.840.1.113883.3.989.2.1.1.19"]]/value[@value='true'])</pre> |
| 2.9  | Does an MAH have access to reports for the same active substance submitted by a third party company? | <p>Yes. Access is provided in accordance with the EudraVigilance Access Policy (revision 3). MAHs have access to ICSRs based on the active substances for medicinal products (reported as suspect/interacting in the ICSR) for which they hold a marketing authorisation in the EEA. This is to support their pharmacovigilance obligations.</p>   |

| Ref. | Question  | Answer   |
|------|---|--|
| 2.10 | <p>If a patient is in an ATU or compassionate use program with a non-approved medicinal product and adverse reactions are reported (per legislation) directly to the local health authority and not to the company, then we are not able to download these cases from EudraVigilance because we would not have an entry in XEVMPD for the product prior to approval. Pre 22 Nov 2017 we would receive the cases directly from the local health authority.</p> | <p>Usually for these types of medicinal products there is no record in the XEVMPD, which is used to determine the substance based access in EudraVigilance. It is therefore not possible to establish, which company should have L2A access. The cases are accessible via level 1 access and the company needs to screen the line listings to identify cases which might relate to a compassionate use programme.</p> <p>If the company already holds a marketing authorisation in the EEA with the active substance contained in the non-approved medicinal product used for the compassionate use programme, then the ICSRs are included for download from EudraVigilance as long as the MAH has entered the authorised medicinal product into the XEVMPD.</p> |
| 2.11 | <p>Is it possible to designate a third party to perform the download of ICSRs?</p>  | <p>An MAH (EU QPPV or appointed deputy) can register one or more users of a third party and grant them with the appropriate access rights so they are able to perform the download of ICSRs associated with that MAH.</p>  |

| Ref. | Question  | Answer  |
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| 2.12 | <p>When an MAH submits a change to the XEVMPD, what is the timeframe for the change to be reflected in the EVWEB download tool?</p> <p>Does this mean that if a product is acquired on for example May 1st, the XEVMPD entry is done by Company A by May 5th, and the EVWEB access is updated to reflect this change by May 8th? Would Company A be able to download on May 8th, all ICSRs for this product from May 1st or May 8th only?</p> | <p>The eLearning video EVM3c explains that dates for ICSR downloads are based on the date of classification of any suspect substance or product reported in the ICSR against Art 57/XEVMPD.</p> <p>The ICSR download is possible the day after a new XEVMPD submission is marked as 'Validated by EMA' (usually up to a week from submission date, provided that the required information is suitable for validation).</p> <p>The organisation that is marked as the XEVMPD owner HQ has access to ICSR data which can be a different organisation to the one that submitted the XEVMPD data (e.g. data submitted by affiliate).</p> <p>The access to ICSRs is not time restricted so the export of ICSRs received prior to the new XEVMPD entry is also supported.</p> |
| 2.13 | <p>The EVM3c training module indicates that ICSRs cannot be downloaded after they have been archived. Is it possible for an MAH to request that ICSRs are moved back into an active state so that the cases can be downloaded?</p>  | <p>The archiving of each <i>download request</i> is performed after 30 days. The ICSRs remain available for download if the MAH makes another request.</p>  |
| 2.14 | <p>When an MAH submits an ICSR to the EMA, does that ICSR also appear for download in EVWEB? Is there a way to filter these cases out?</p>  | <p>The ICSR download function automatically excludes same sender ICSRs from the download.</p>   |

| Ref. | Question  | Answer  |
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| 2.15 | <p>Are users restricted to see the downloads that they have requested for themselves?</p> <p>Is it possible for an EVWEB user to see what has been downloaded by other users for that same company setup e.g. can everyone in Company A HQ see what other users in COMPANY A HQ have downloaded?</p>  | <p>The ICSR download manager shows all requests made by the same organisation, therefore a user with the appropriate rights can see requests made by other users within their organisation.</p>   |
| 2.16 | <p>As an MAH, we are trying to plan for the increased volume of cases anticipated due to the upcoming centralised ICSR Download process. Is there a particular algorithm being used to estimate anticipated case volume? What is the estimated volume that the EMA is anticipating to receive on a daily basis? How was this estimated?</p> | <p>The number of serious ICSRs being sent to EudraVigilance should in principle not change based on the current reporting rule, only who reports the ICSR to EudraVigilance changes.</p> <p>The estimation for non-serious EEA cases is around 2-3 non-serious cases for every serious EEA case.</p> <p>This estimate is based on overall figures seen in PSURs. The EMA estimated to receive around 1,000 serious EEA ICSRs and 3,000 non-serious EEA ICSRs daily.</p> |

| Ref.  | Question   | Answer  |        |                       |            |  |  |  |           |                    |                |                        |                |               |                    |                |   |  |  |           |                    |                |                        |                |
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| 2.17  | <p>Do local NCAs also report non-serious cases to EudraVigilance?</p> <p>Can an MAH expect non-serious cases from NCAs to also be available for export from EVWEB?</p> | <p>The EudraVigilance submission requirements for valid unsolicited and solicited ICSRs reported by healthcare and non-healthcare professionals [DIR Art 107(3), 107a(4)] are as follows:</p> <table border="1"> <thead> <tr> <th>Origin</th> <th>Adverse reaction type</th> <th>Time frame</th> </tr> </thead> <tbody> <tr> <td colspan="3" style="text-align: center;"><b>Marketing authorisation holders</b></td> </tr> <tr> <td rowspan="2"><b>EU</b></td> <td><b>All serious</b></td> <td><b>15 days</b></td> </tr> <tr> <td><b>All non-serious</b></td> <td><b>90 days</b></td> </tr> <tr> <td><b>Non-EU</b></td> <td><b>All serious</b></td> <td><b>15 days</b></td> </tr> <tr> <td colspan="3" style="text-align: center;"><b>Competent authorities in Member States</b></td> </tr> <tr> <td rowspan="2"><b>EU</b></td> <td><b>All serious</b></td> <td><b>15 days</b></td> </tr> <tr> <td><b>All non-serious</b></td> <td><b>90 days</b></td> </tr> </tbody> </table> <p>ICSR downloads include both serious and non-serious as per the above reporting requirements (see also EudraVigilance Access Policy revision 3).</p> | Origin | Adverse reaction type | Time frame | <b>Marketing authorisation holders</b> |  |  | <b>EU</b> | <b>All serious</b> | <b>15 days</b> | <b>All non-serious</b> | <b>90 days</b> | <b>Non-EU</b> | <b>All serious</b> | <b>15 days</b> | <b>Competent authorities in Member States</b> |  |  | <b>EU</b> | <b>All serious</b> | <b>15 days</b> | <b>All non-serious</b> | <b>90 days</b> |
| Origin  | Adverse reaction type  | Time frame  |        |                       |            |  |  |  |           |                    |                |                        |                |               |                    |                |   |  |  |           |                    |                |                        |                |
| <b>Marketing authorisation holders</b>        |  |   |        |                       |            |  |  |  |           |                    |                |                        |                |               |                    |                |   |  |  |           |                    |                |                        |                |
| <b>EU</b>                                     | <b>All serious</b>   | <b>15 days</b>  |        |                       |            |  |  |  |           |                    |                |                        |                |               |                    |                |   |  |  |           |                    |                |                        |                |
|   | <b>All non-serious</b>   | <b>90 days</b>  |        |                       |            |  |  |  |           |                    |                |                        |                |               |                    |                |   |  |  |           |                    |                |                        |                |
| <b>Non-EU</b>                                 | <b>All serious</b>   | <b>15 days</b>  |        |                       |            |  |  |  |           |                    |                |                        |                |               |                    |                |   |  |  |           |                    |                |                        |                |
| <b>Competent authorities in Member States</b> |  |   |        |                       |            |  |  |  |           |                    |                |                        |                |               |                    |                |   |  |  |           |                    |                |                        |                |
| <b>EU</b>                                     | <b>All serious</b>   | <b>15 days</b>  |        |                       |            |  |  |  |           |                    |                |                        |                |               |                    |                |   |  |  |           |                    |                |                        |                |
|   | <b>All non-serious</b>   | <b>90 days</b>  |        |                       |            |  |  |  |           |                    |                |                        |                |               |                    |                |   |  |  |           |                    |                |                        |                |
| 2.18  | <p>Are there means (other than looking at the export history) of tracking or having an overview of what ICSRs have been downloaded by an MAH?</p>                      | <p>Apart from L2B requests (ICSRs including case narratives), ICSRs exported by an MAH are not tracked by the EMA. MAHs can store a copy of their downloaded zip files as a record of what was downloaded on each day.</p>  |        |                       |            |  |  |  |           |                    |                |                        |                |               |                    |                |   |  |  |           |                    |                |                        |                |
| 2.19  | <p>When EU assessment is present, are two assessments by the reporter and the MAH, be also present or not?</p>   | <p>In accordance with the specific data elements as defined in the EudraVigilance Access Policy (revision 3), the information as provided by the sender, are provided in the ICSRs exported.</p>  |        |                       |            |  |  |  |           |                    |                |                        |                |               |                    |                |   |  |  |           |                    |                |                        |                |

| Ref. | Question   | Answer  |
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| 2.20 | <p>The published material by the EMA states that an overview of duplicate masters with their linked duplicates can be made available to an MAH.</p> <p>Can you please provide details on how we can obtain/request this overview and what details it provides?</p> | <p>The "Master" ICSR (mastericsr) cases are included as part of the ICSR download in EVWEB.</p> <p>Each master case contains the case number &amp; Safety Report ID of all of the associated duplicates, in the "Other case identifiers" section (ICH E2B(R3) C.1.9.1).</p> <p>The field "Source(s) of the case identifier" (C.1.9.1.r.1) will start "EVDUP#" followed by the sender identifier of the sending organisation. The case number will be in C.1.9.1.r.2 (Case identifiers).</p> <p>In addition, an EVDAS query which will show MAHs which of their cases are grouped under a master is being developed and is to be released after November 2017. The EMA will communicate closer to the time when it will be released.</p> <p>For technical details related to the specifications of master cases, please refer to the EU ICH E2B(R3) ICSR Implementation Guide.</p> |
| 2.21 | <p>If a masterichicsr is deleted because it is no longer valid (i.e. they are not true duplicates), would the MAH receive nullification for the deleted masterichicsr?</p>   | <p>Nullification ICSRs are included for both masters and non-masters. Master cases (message type MASTERICHICSR) can only be nullified by the EMA, and once they are nullified, the underlying duplicates are reclassified so that they are no longer grouped together.</p>  |

| Ref. | Question   | Answer   |
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| 2.22 | <p>For stakeholder group III, access level 2B, are there differences in access based on which level the individual cases are coded (substance vs product)?</p> <p>Example:</p> <p>Company A, Product A, substance Paracetamol</p> <p>Company B, Product B, substance Paracetamol</p> <p>1: If a case is coded on Product A, can Company B get access to level 2a data?</p> <p>2: If yes to 1, then can Company B get access to all level 2b data (after formal request)?</p> <p>If a case is coded on Paracetamol, we presume that both Company A and Company B can access level 2A data. Can both company A and B get access to all level 2B data (after formal request)?</p> | <p>Both EVWEB and EVDAS provide access to MAHs at the level of the active substance using the highest level in the hierarchy of the XEVMPD. This is known as the 'Active substance high level' grouping. MAHs with a product containing an active substance can access levels 2A and 2B for the cases where the substance (or the product containing the substance) is reported as suspect/interacting. This is regardless of the medicinal product and regardless of the sender of the ICSRs.</p> <p>For the example on paracetamol, both companies A and B have access to level 2A and 2B for the cases where paracetamol is reported as suspect/interacting. Moreover, company A has level 3 access for the cases they have sent and company B has level 3 access for the cases they have sent. For the MLM cases, company A and B will get also level 3 access.</p> <p>The level 2B 'request' is automated in the system (EVWEB). Companies have to select the reason for the request and confirm their agreement with the confidentiality undertaking. These steps are fully integrated in EVWEB and no stand alone or separate request has to be submitted to the EMA.</p> <p>See also question 2.1.</p> |

| Ref. | Question   | Answer   |
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| 2.23 | Does the ICSR batch download functionality only include ICSRs with an active substance for which a MA is hold in EEA but exclude all ICSR submitted by another MAH or by the MAH itself?                       | <p>The ICSR download function excludes all the ICSRs submitted by their own organisation. The exclusion of MAH ICSRs is based on the ICSR message sender ID which is based on the Headquarter ID and any of the associated affiliate IDs.</p> <p>The download however includes all ICSRs submitted by any other organisation that matches the active substances, for which they hold an EEA MA.</p> <p>See also Questions 2.1 &amp; 2.14.</p>  |
| 2.24 | Once we have submitted in EVWEB using manual data entry, are the submissions in R3 format? - so this means if we move to gateway submission in the future the submission must be R3 too, as we cannot go back? | <p>EVWEB creates E2B(R3) messages only. If an organisation implements a pharmacovigilance system that only supports E2B(R2) submissions this means that follow-up submissions are in the less well-structured E2B(R2) format.</p> <p>Organisations are requested not to do this as this reduces the quality of the information between versions of an ICSR.</p>  |
| 2.25 | Which active substances / products' information can be accessed as MAH in the Levels 1/2A/2B/3?  | <p>The details of what information is displayed at Level 1 and Level 2 are described in the <a href="#">EudraVigilance Access policy (revision 3)</a>. An e-Learning course is <a href="#">here</a>.</p> <p><u>As a quick summary:</u></p> <ul style="list-style-type: none"> <li>• Level 3 gives full access to the information as submitted;</li> <li>• Level 2 gives the verbatim substance and product information even if not yet classified;</li> <li>• Level 1 gives access to the product name for CAPs and substance names for products authorised through other procedures; no access is given to unclassified medicinal product and substance information.</li> </ul> |

| Ref. | Question  | Answer   |
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| 2.26 | How can narratives be downloaded? Do we need to take one of the training sessions in person to get access to Narratives (Level 2B?)   | User access to Level 2B is granted by the QPPV or deputy QPPV within your organisation. <a href="#">This eLearning course</a> shows how to make a Level 2B request   |
| 2.27 | Pharmacovigilance obligations report (L2A) is not filtering by active substance. While testing the EV test area for ICSRs download, we came across the following issue: We created a query for PV obligations reports (L2A) based on start and end date and we downloaded the bulk received.<br><br>We tried querying the system by adding the substance search criteria, with one of the substances that were included in the bulk that was downloaded from the previous query, but it returned 0 results. | Test product and substance data (SUBSTANCE-L2A & Product-L2A) was automatically generated to give MAHs some L2A/B access to ICSR data in the XCOMP system.<br><br>However, active substance groups (including SUBSTANCE-L2A) have not been created for use in the download filters in XCOMP. The production system uses all the validated XEVMPD data and all the substance groups created for L2A/B access and eRMRs. |
| 2.28 | Is it possible to exclude ICSRs with other MAHs tradenames from ICSR download for a specific active substance?  | No, the download is matched against active substances.   |

| Ref. | Question   | Answer  |
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| 2.29 | If a narrative is downloaded via L2B access is it allowed to include this in the company safety database?  | The MAH must ensure that EU data protection legislation is adhered to when the ICSR data based on L2B access are processed and stored in their pharmacovigilance systems. This applies to systems established within and outside the EEA.   |
| 2.30 | Is it possible to download the ICSRs by sorting according to country of occurrence?  | A filter for primary source country is available in EVWEB.  |
| 2.31 | During the ICSR download from EudraVigilance, are only medicinal products specific to the company of the person logged into EudraVigilance downloaded if no other settings are selected? | The ICSR download is linked to the Organisation Headquarter ID. Only users registered as part of the HQ can make L2 download requests and for all medicinal products in the XEVMPD associated with that HQ.<br><br>Question 2.22 explains in detail how ICSRs are made available based on the active substance. |
| 2.32 | Can you specify if nullflavors are used in ICSRs from EVWEB to mask date values (i.e. date of batch transmission) or UCUM values?  | The EU and ICH implementation guides indicate for which fields and what types of nullflavors are permitted.   |
| 2.33 | Are all elements not available for level 2A users masked in ICSRs by nullflavors?  | In most situations the data elements are not populated in the XML if no access is permitted. If a field is mandatory according to the XSD schema a nullflavor is used.  |
| 2.34 | Can we copy and paste from EVWEB? We anticipate a low volume so I am trying to find a bridging manual work around without having to validate the xslt converter.                         | E2B(R3) files can be imported into the EVWEB workspace and can then be printed in human readable formats.<br><br>Please see the <a href="#">EVWEB user manual</a> for more details  |

| Ref.                     | Question   | Answer   |
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| 2.35                     | Are ICSRs re-routed as single ICSR messages only or can we expect to receive messages with multiple ICSRs?     | <p>ICSRs are normally re-routed individually as single XML files as most submissions to EudraVigilance are single ICSRs.</p> <p>However, in the event that a batch of ICSRs is received by EMA in one file and more than 1 ICSR within the batch is matching the re-routing rules for an NCA, the relevant ICSRs within that batch of ICSRs re-routed to the relevant NCAs within a single XML file.</p>   |
| 2.36                     | Does EMA follow-up on missing ACKs on re-routed ICSRs?   | <p>The EU Implementation Guide explains the number of the retries that will be attempted as follows: "NCAs should return acknowledgements for re-routed ICSRs within 48 hours of the initial receipt. If no acknowledgement is received within 48 hours, EudraVigilance will automatically resubmit the re-routed ICSRs."</p> <p>First submission is 48 hours; second attempt is 24 hours third attempt is 24 hours. If not it is 6 days before the service desk contacts the NCA. EudraVigilance resubmits ICSRs up to a maximum of three attempts following the initial re-routing if no acknowledgement has been returned.</p> <p>After the maximum number of resubmissions has been reached, the NCA is contacted to confirm if they are experiencing technical issues."</p> |
| 2.37<br><b>(Updated)</b> | Are current MedDRA versions accepted in the new XCOMP environment? Is XCOMP updated with every MedDRA release? | Yes, the current MedDRA version and one previous version (21.1 & 21.0 as of 5 November 2018). As with PROD, XCOMP is updated with every MedDRA release.  |
| 2.38                     | Are the re-routing rules from EV to NCAs considering transmission date or receipt date?                        | Re-routing is based on the primary-source country, further details are available in the <a href="#">EU Implementation guide</a> .  |

| Ref. | Question   | Answer   |
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| 2.39 | If an MAH identifies case reports under the signal detection process, that requires access to the case narrative, they are able to retrieve the ICSRs from the EVWEB ICSR export screen using the filter Level 2B – please confirm that the download process will bypass the automatic removal of ICSRs cases sent to EV by the MAH in question? | L2B requests require that the requester enters the worldwide case ID(s) for the ICSR(s) required, same sender (Level 3) ICSRs are excluded from such requests as these WW case IDs should be in the requestor's own database.<br><br>However, if the requestor wishes to view their own cases in EudraVigilance this can be done through a search for the case in the ICSR search section of EVWEB, from there the requestor can view the case without having to complete the reason for the request and the confirmation of the confidentiality agreement |
| 2.40 | Can a company continue to report on a partner's behalf even though we don't have access to the product in EV since we are not the MAH in the EU and don't hold the marketing authorisation?  | Yes. Any organisation can report ICSRs related to any medicinal product.   |
| 2.41 | Is it possible to extract for one high level substance group and for one signal all corresponding narratives? (level 2B) (by batch)  | Yes. Level 2B requests can be made by entering a list of worldwide unique case identifiers for which the corresponding ICSRs can be downloaded in one zipped file.   |
| 2.42 | Is L2B access (EVWEB) for subcontractors restricted to a limited period of time?   | The EU QPPV and trusted deputy will have the ability to grant and remove a user's Level 2B access.<br><br>User access permissions are managed by the EU QPPV/Deputy QPPV through the secure area of EudraVigilance under "manage your profile".  |

| Ref. | Question   | Answer   |
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| 2.43 | <p>In relation to the search of cases in EVWEB we would appreciate some guidance on the following scenario: an MAH had recently obtained an authorisation for a new indication with the corresponding new dosing and dosage form.</p> <p>The active substance was already approved some time ago. Is it possible to narrow the "active substance search" with the help of the following filters: "indication for use" and/or "new dosage form" and "dosing" characteristics to narrow the research results</p> | <p>The download function is based on the EudraVigilance Access Policy L2A. Access is based on the active substance for medicinal products, for which an MAH holds a marketing authorisation.</p> <p>The dosage form field in ICSRs is currently a free text field and therefore a filter would be an unreliable way of identifying specific medicinal products. The indication stated in ICSRs is captured as reported by the primary source, which may not match the MedDRA terms of the authorised indication; this information is therefore not reliable to retrieve all cases.</p> <p>The country of the primary source can however be used to exclude countries where a medicinal product is not authorised. However, it should be noted that a patient can obtain medicinal products in another country.</p> |
| 2.44 | Which formats are case narratives downloadable for Level 2B access? Excel, Word, XML?  | ICSRs with case narratives can be exported in E2B(R3) XML format.  |
| 2.45 | If an MAH is going to retrieve the ICSRs sent to EV from all NCAs, will it be still mandatory to send ACK messages?  | MAHs must not send acknowledgements for any ICSRs downloaded from EudraVigilance.  |

| Ref. | Question  | Answer   |
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| 2.46 | If a case was submitted to an NCA prior to 22 November 2017 and needs to be nullified after 22 November, should the nullification be sent to EudraVigilance?                                      | <p>A new classification of EEA nullification requests has been added to allow MAHs to submit nullifications for cases previously sent to NCAs.</p> <p>For post-authorisation ICSRs, the nullification report should be submitted to the EudraVigilance Post authorisation Module (EVPM).</p> <p>Please see the <a href="#">EU implementation guide</a> for further details.</p> <p>For ICSRs related to suspected unsuspected serious adverse reactions (SUSARs) from clinical trials which were previously submitted to an NCA, the nullification report should be also sent to this NCA.</p> |
| 2.47 | Please confirm that the ICSR form will only show case narratives for the MAH originated ICSRs, for non-MAH originated ICSRs you need to request case narratives from EVWEB using level 2b access? | <p>ICSR forms level 1 and 2A do not contain a case narrative. The narratives are provided in the ICSR form level 3 and for level 2B access in EVWEB.</p> <p>For more information about the ICSR form, please consults the <a href="#">ICSR form manual</a></p>   |
| 2.48 | Is it possible to copy and paste WWIDs from the line listing (EVDAS) where case narratives are not visible and thereby need to be requested under level 2B from EVWEB?                            | <p>It is possible to copy and paste World Wide Unique Case identifiers. Comma delimiters need to be used when pasting a list of case IDs.</p>  |
| 2.49 | Can EVWEB be opened in Internet Explorer?   | <p>Yes. The supported browsers to be used to access EVWEB are the most recent version of Google Chrome, Internet Explorer and Mozilla Firefox. Some users have reported problems with using the ICSR download section when using Internet Explorer, therefore the EMA recommends using Google Chrome or Mozilla Firefox for this functionality.</p>  |

| Ref. | Question  | Answer   |
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| 2.50 | <p>Is there a limitation of numbers of users that the QPPV can designate to have Level 2B access?</p> <p>Is this number separate to those users registered with the EVDAS scientific role?</p>  | <p>There is no limit for the number of users the EU QPPV can designate to have Level 2B access. It is just an EVWEB user permission.</p> <p>This is a separate permission for the EVWEB interface; it is not associated with the EVDAS roles.</p>  |
| 2.51 | <p>Please confirm that a user NOT registered for EVDAS scientific role can still have Level 2B access providing they are registered in EV at HQ level?</p>  | <p>This is correct. This is a separate permission for the EVWEB interface and requires that the user is registered at HQ level by the EU QPPV.</p>   |
| 2.52 | <p>How will access to L2B ICSRs work with regards to QPPV oversight and accessing EVWEB to download ICSRs with case narratives – will the prompt screen still appear upon request for the user to confirm that the download is for the purposes of signal detection activities?</p> | <p>The individual user that are granted L2B access by the EU QPPV has to agree to the confidentiality undertaking and also provide the reason for the request each time they need to review case narratives.</p> <p>This is done by entering the reason for the request and by confirming the confidentiality undertaking using a tick box in the interface.</p>   |
| 2.53 | <p>Is there a character limit to the filters for companies that are responsible for over ~1000 medicinal products?</p>  | <p>There is an effective limit of approximately 1,400 substance combinations.</p> <p>The exact number may depend on how many substances there are in each combination.</p> <p>Users should be aware that the larger the filter the longer it will take to run the query. Therefore we recommend that, where possible, you limit your filters to no more than 500 substance combinations for each query</p> |

| Ref. | Question  | Answer  |
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| 2.54 | <p>Can you confirm the expectation that in Germany the local 'graduated plan officer' is to review all domestic post marketing cases before they are submitted to EV in order to be able to provide his/her own assessment as necessary?</p> <p>In practice, could this be done through listings or other means, rather than the German cases being submitted by the German local team to EV? The central reporting allows companies to centrally send cases from one central point (in our outside the EU) to EV, simplifying the process. But if the cases need to be reviewed by the German 'graduated plan officer', this would complicate the process.</p> | <p>It is correct that the German drug law states that the graduated plan officer is to collect and evaluate notifications on medicinal product risks that have become known and co-ordinate the necessary measures and that this article (AMG §63a) is not affected by the changes coming into effect on November 22nd.</p> <p>However, even now in most companies the graduate plan officer does not perform these activities himself/herself but has delegated this to EU/global HQ.</p> <p>As long as the delegation is documented in writing and there is an appropriate oversight mechanism in place this practice is acceptable to us.</p> <p>Regarding the reporting obligation, it is correct that the oversight mechanism should enable the graduated plan officer to take action if a case would otherwise be late.</p> |

| Ref. | Question   | Answer   |
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| 2.55 | <p>Is there a guidance document available or planned regarding the download functionality from EV Web, specifically, the filter functionality?</p> <p>Is a list of active substance group definitions which can be used for filtering available?</p> | <p>An eLearning course (<a href="#">EV-M3c: EV Reporting process for users: Export functions in EVWEB</a>) and a <a href="#">user manual</a> are published on the EMA website. Please see chapter 2.11.3. <i>ICSR Download</i> of the user manual for more information on the filters available.</p> <p>The list of active substance groups associated with a specific MAH's organisation ID can be obtained in EVDAS. Instructions are provided in the "<a href="#">Marketing Authorisation Holders' access via the EudraVigilance Data Analysis System (EVDAS)</a>" <a href="#">user manual (EV-G1a)</a>, chapter 6 "The EVDAS active substance grouping report".</p>                            |
| 2.56 | <p>Is it still possible to send XMLs in R2 format using the "IMPORT" option in EVWEB for Web Trader users? If yes, are some additional amendments needed for the XML prior sending?</p>  | <p>Yes. E2B(R2) ICSRs can be imported into EVWEB through the use of the workspace area.</p> <p>From the workspace, the ICSR can be moved into the "create and send area" of EVWEB, by selecting the follow-up option.</p> <p>However, by doing this the ICSR will be converted into the E2B(R3) format and additional fields may need to be completed or amended before sending, in order to comply with the E2B(R3) business rules.</p> <p>Users should note that the seriousness, which will be at case-level in the original R2 ICSRs, will be copied to every reaction in the R3 version. They should therefore review these to ensure that correct reaction-level seriousness is reported</p> |
| 2.57 | <p>The XCOMP environment was made available in June. Is it correct that E2B(R2) XML cannot be sent through testing environment?</p>  | <p>The XCOMP environment accepts both E2B(R2) and E2B(R3) ICSRs.</p> <p>These can be sent by means of the EudraVigilance Gateway or the EV post function.</p>  |

| Ref. | Question   | Answer  |
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| 2.58 | Testing for EV POST function users is mandatory, however for vendors it can be done just once and not for each client/MAH separately. Is this also the case if clients are hosted in separate instances of the same database within the same vendor company?   | Once a vendor or third party service provider has successfully completed testing with the EMA, further full testing with EMA QA testing by clients is not required as long as the same version of software and configuration files are being used. Step 4 and Step 5 testing should still be performed by the organisation in the XCOMP system. The organisation should then inform the EMA that this self-testing was successful with no issues encountered. If customisations are made to pre-tested software then then full step 5 testing is required |
| 2.59 | Regarding service contractors and the download of authority cases: Can user access be restricted in a way that a user of the service contractor does not see any cases which have been submitted by an MAH/client? If a user is registered without any access rights (Rights for XEVMPD: no access right, Rights for ADR: no access right, User Rights for EVDAS: no access right), is the user able to use the ICSR Download manager? | <p>Users associated with affiliates of the HQ cannot see L2 data. They are only able to see data sent by the affiliate.</p> <p>Users registered at the HQ level are be able to see all data including L2 data.</p>  |

| Ref. | Question   | Answer  |
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| 2.60 | <p>It is our understanding that narratives are not available as standard from EudraVigilance Download Area for cases reported from NCAs within the EEA.</p> <p>What is the rationale for this?</p>                                       | <p>It is correct that case narratives are not part of the normal L2A ICSR downloads.</p> <p>The EudraVigilance Access Policy sets out the data elements and rationale for access to fields such as the case narrative.</p> <p>The dedicated <a href="#">"Access to EudraVigilance data" webpage</a> provides further information.</p>             |
| 2.61 | <p>When cases are downloaded from EVWEB, what will be present in the receiver ID tag?</p>  | <p>The receiver ID will be set to the organisation ID of the user logged into EVWEB.</p>  |
| 2.62 | <p>With regard to CT SUSAR reporting, can EMA clarify whether reports sent to NCAs are processed first by EV (generating acknowledgement) and then forwarded to NCAs or simply forwarded by the EV gateway?</p>                          | <p>The current SUSAR reporting process will not change until the application of the Clinical Trial Regulation.</p> <p>If the NCA is the intended recipient, the ICSR (SUSAR) is sent to the NCA directly through the gateway.</p> <p>Acknowledgments are generated by the NCA and returned via the gateway to the sender of the ICSR (SUSAR).</p> |
| 2.63 | <p>Case download: When an MAH has license agreements with other EU MAHs, will there be a possibility to act on behalf of all in terms of downloading? Or will partners have to split that activity in order to get the full picture?</p> | <p>The access to ICSR data for downloading depends on MAH owner HQ ID associated with the medicinal products and their active substances as entered in the XEVMPD.</p> <p>You will need to take this into account as part of your arrangements with your licensing partners.</p>  |

| Ref. | Question  | Answer   |
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| 2.64 | Case handling and contents: How do amendments work for cases that have originally been submitted to individual EU NCAs? There could very well be an initial report sent to EMA that would qualify as an amendment report. | The amendments will be handled the same as any other submission of a valid ICSR.<br><br>If different organisations have previously sent the report to EudraVigilance, they will be combined under a master case.   |
| 2.65 | Submission requirements: How are the submissions of downgraded reports handled? If a downgrade leads to an invalid case, can that still be submitted to EMA without violating E2B rules?                                  | If 'downgrade' means from serious to non-serious the case is still a valid ICSR and the follow-up can be sent without being rejected.<br><br>If 'downgrade' means that a case is no longer valid (e.g. there were not actually any adverse reactions) and it needs nullification then see question 2.51. |
| 2.66 | EVWEB ICSR download:<br><br>Does EMA publish only ICSRs for download from the EEA (or also from other countries/regions)?   | The download ICSR function is for EEA cases only. MAHs do also have access to all worldwide data in EudraVigilance through the ICSR search function and EVDAS. This is in support of their pharmacovigilance obligations including signal management.  |

| Ref. | Question  | Answer  |
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| 2.67 | <p>Regarding the ICSRs reported by NCAs: could you give us more details regarding the ICSR download functionality of EVWEB? Is it a new tool of EVWEB?</p> <p>What will be the mandatory frequency for downloading the cases?</p> | <p>The download function is part of EVWEB. An eLearning course (<a href="#">EV-M3c: EV Reporting process for users: Export functions in EVWEB</a>) and a user manual are published on the "<a href="#">EudraVigilance training and support</a>" webpage.</p> <p>Please see chapter 2.11.3. <i>ICSR Download</i> of the <a href="#">EVWEB user manual</a> for more information</p> <p>The EudraVigilance System provides access to reports of suspected adverse reactions related to medicines, which occurred in the EEA via the EudraVigilance ICSR download function. This is referred to as Level 2A access and MAHs can download ICSRs for all active substances (reported as suspect or interacting), for which they hold a marketing authorisation in the EEA. In accordance with the <a href="#">EudraVigilance Access Policy</a>, Level 2A access also provides the name of the medicinal product as reported by the primary source (if provided). On this basis the MAH can review the ICSRs and determine "ownership" related to the medicinal products, for which they hold a marketing authorisation.</p> <p>Article 24 of the Regulation (EC) 726/2004 states that the EudraVigilance database "shall also be accessible to MAHs to the extent necessary for them to comply with their pharmacovigilance obligations".</p> <p>Such access is provided based on the Level 2A downloads to facilitate the oversight of the overall safety profile of an active substance independent of the route of reporting by the primary source either via an NCA or an MAH in the EEA.</p> |
| 2.68 | <p>Is the list of substances covered by EVDAS the same that the list of substances covered by MLM?</p>  | <p>The MLM service covers 300 substances and 100 herbal substance groups. EVDAS provides data based on all ICSRs submitted to the EudraVigilance Post-Authorisation Module (EVPM) by any organisation for the selected active substance, where the substance (corresponding medicinal product) is reported as suspect or interacting. This includes MLM cases.</p>  |
| 2.69 | <p>If an ICSR is submitted in E2B(R2) format, are the ACKs returned in E2B(R3) format?</p>  | <p>If an organisation sends a valid E2B(R2) XML file, it will receive acknowledgements in E2B(R2) format. If an organisation sends a non-valid XML file, EudraVigilance will return an E2B(R3) acknowledgement since it will not be able to identify if the file was intended to be in E2B(R2) format.</p>  |

| Ref. | Question  | Answer  |
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| 2.70 | When were the new sample files with attachments published?  | <p>The XCOMP system was updated on the 21 September 2017 and the compression algorithm was changed from RFC1950 to RFC1951.</p> <p>The test files were updated and republished accordingly.</p>   |
| 2.71 | Currently, MAHs are expected to obtain ICSR information by downloading these cases from EVWEB and uploading into their database. Are there any efforts being made going forward for a future state such that EudraVigilance would "push" this data out to NCAs/MAHs electronically? | <p>Technical solutions for MAHs for a potential future automation are being investigated but currently there is no firm date for implementation of such solutions.</p> <p>For NCAs in the EEA, the messages are already automatically rerouted.</p>   |
| 2.72 | What is the process if a download from EVWEB fails?   | <p>If the EudraVigilance system is not available, the EMA service desk will send out an announcement to inform MAHs about the potential downtime. Instructions on the process to be followed in case of system failure are provided in the <a href="#">EU ICSR Implementation Guide</a>.</p> <p>If you are having a specific technical issue you should contact the <a href="#">EMA service desk</a> for support.</p> |
| 2.73 | Where can E2B(R3) sample files including masterichcsr files be found?   | <p>Examples are already published on the dedicated "<a href="#">EudraVigilance change management</a>" webpage as part of the testing files: <a href="#">EU E2B(R3) testing files</a>.</p> <p>Organizations can also use EVWEB in the XCOMP environment to create their own E2B(R3) test files, which can be further utilised to perform backwards and forwards conversion testing.</p>                                |

| Ref. | Question  | Answer   |
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| 2.74 | <p>How are ICSRs where the reported medicinal product information has been reclassified distributed: are MAHs able to download cases with original coding as well as EMA reclassified information?</p> <p>As far as we are aware, EMA reclassified cases are not distributed to NCAs.</p> | <p>The <a href="#">EU ICSR Implementation Guide</a> explains how the drug names are classified against the XEVMPD and how this information is provided in the E2B(R3) XML files.</p> <p>For details refer to sections I.C.6.2 "Classification of Medicinal Product Information" &amp; I.C.6.2.1 "Classification of medicinal products in the interim period before ISO IDMP is available".</p> <p>The rerouting of ICSRs to NCAs is performed without changing what was originally reported. Once the ISO IDMP standards are implemented, NCAs are able to choose to receive ICSRs classified against the ISO IDMP set of standards.</p> |
| 2.75 | <p>What is the maximum size of an R3 XML that EudraVigilance can accept?</p>  | <p>The file size limit 20Mb is published in the <a href="#">EU ICSR Implementation Guide</a> (page 33) section: I.C.3.2 Individual Case Safety Report (ICSR).</p>  |
| 2.76 | <p>How can we obtain the additional documents attached to a E2B(R3) ICSR with the BFC tool? For example, in the case the EMA provides a literature case with attachments.</p>   | <p>In accordance with the <a href="#">EudraVigilance Access Policy</a>, E2B(R3) ICSRs downloaded from EudraVigilance do not include attachments.</p>   |
| 2.77 | <p>Does the EMA consider "false" as a valid serious criterion value in an E2B(R3) file?</p>   | <p>The EudraVigilance system supports the Boolean datatype and the nullflavor for this field, therefore "false" can be used.</p>   |
| 2.78 | <p>How to use UCUM list published by EMA in July 2017? It is confusing which units shall be used for Dosage units, Strength and Lab data?</p>   | <p>Any value in the published UCUM list can be used in dosage, strength and lab unit fields. The columns, IS_APPLICABLE_LAB_TEST, IS_APPLICABLE_STRENGTH &amp; IS_APPLICABLE_DOSAGE indicate if the unit is suitable for those fields if it has the value 1. The value 0 indicates that the unit is not suitable for that specific field, and leads to a data quality warning message in an acknowledgement returned.</p>  |

| Ref. | Question   | Answer  |
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| 2.79 | What is the average size of the E2B(R3) files that are available for download in EVWEB?  | Fully structured E2B(R3) files are typically around 10-15% larger than the equivalent E2B(R2) files. Note that ICSRs downloaded from EudraVigilance do not contain a case narrative and therefore file sizes are probably be around the same.   |
| 2.80 | When Jpeg files are embedded within E2B(R3) files, the size of the file can reach 30 Mb. Is it likely to have such files available in EVWEB?   | <p>The file size limit 20Mb is published in the <a href="#">EU ICSR Implementation Guide</a> (page 33) section: I.C.3.2 Individual Case Safety Report (ICSR).</p> <p>In addition, the maximum size of an attachment file is restricted to 15Mb. The sender of attachments should ensure that an appropriate resolution and format for images and documents is chosen to ensure that the file size is not too large.</p> |
| 2.81 | If an MAH only has MAH status in one EU country (e.g. Spain) for an active substance, will the MAH receive ICSRs in download only for the occurrence country where the marketing authorisation is held or cases from all EU countries? | <p>The MAH will have access to download all EEA ICSRs for that same active substance.</p> <p>The primary source for regulatory purposes (filter name: "Primary Source Country" can be used to filter only for the country of interest. This field is used rather than where the patient was at the time of each reaction in the ICSR. Note: occurrence country for E2B(R3) ICSRs is at reaction/event level.</p>        |

| Ref.               | Question  | Answer   |    |    |     |      |    |       |                    |    |
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| 2.82               | As per ICH E2B(R3), the values allowed for data element "Other Case Identifier" (C.1.9.1) are "True" and null flavour "NI"; but in EV XCOMP, the value "No" is also available. In which scenario should the value "No" & Null flavour "NI" shall be selected? | <p>To support the migration of E2B(R2) data and the continued use of E2B(R2) ICSRs in EV, the value "false" for Boolean values is also allowed for the submission of E2B(R3) data to EudraVigilance as the data is stored as received.</p> <p>The following values are equivalent in each format:</p> <table border="1"> <thead> <tr> <th>R2</th> <th>R3</th> </tr> </thead> <tbody> <tr> <td>Yes</td> <td>True</td> </tr> <tr> <td>No</td> <td>False</td> </tr> <tr> <td>Blank/null/missing</td> <td>NI</td> </tr> </tbody> </table> <p>In accordance with the <a href="#">EudraVigilance Access Policy</a> the data is provided as captured in the database. Therefore an E2B(R2) reported value as "No" is not exactly the same as Blank/null/missing in an E2B(R3) file. It is left to the organisation downloading data to decide if they want to interpret E2B(R3) files with "False" as being E2B(R3) "NI" when storing the data in their own system.</p> | R2 | R3 | Yes | True | No | False | Blank/null/missing | NI |
| R2                 | R3  |  |    |    |     |      |    |       |                    |    |
| Yes                | True  |  |    |    |     |      |    |       |                    |    |
| No                 | False   |  |    |    |     |      |    |       |                    |    |
| Blank/null/missing | NI  |  |    |    |     |      |    |       |                    |    |
| 2.83               | When the MAH downloads cases from EudraVigilance, what is the 'sender' ID? Is this the EV ID or the regulatory authority that submitted it to EudraVigilance?   | The Sender is set as either EVHUMAN or MLMSERVICE for literature cases entered by the EMA. The receiver ID is set as the Headquarter organisation ID that is downloading the ICSRs.  |    |    |     |      |    |       |                    |    |

| Ref. | Question   | Answer   |
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| 2.84 | <p>In an E2B(R2) file submitted with 6 adverse reactions and a positive re-challenge for 3 adverse reactions, we are seeing the positive re-challenge value coming back for all 6 events.</p> <p>Can EMA confirm if this is the process for the EMA E2B(R2) to E2B(R3) conversion?</p> | <p>EudraVigilance stores E2B(R2) data in R2 data fields; in addition E2B(R3) data is stored in R3 fields. Data that is common to both R2 and R3 is stored in the same fields.</p> <p>The BFC tool is not used in EudraVigilance.</p> <p>The BFC tool should not be used for creating E2B(R3) files from R2 ICSRs to load into an E2B(R3) system. If you wish to report an issue in the published BFC tool, please submit a service desk request and include example test files that illustrate the issue.</p>  |
| 2.85 | <p>What is the archive timing for ICSR files after which they will no longer be available? Is there a process that an MAH can obtain access to an archived ICSR after that time period has elapsed?</p>  | <p>Each download request is archived after 30 days. The archive process only applies to the ZIP files that have been created as part of an L2A or L2B request.</p> <p>If an MAH wishes to download an ICSR that has been archived, the MAH needs to submit a new request with the same date period or quote the same Worldwide case IDs.</p>   |
| 2.86 | <p>When an E2B(R2) file is converted to E2B(R3), the case level seriousness criteria appears to be applied to all events whether they are serious or non-serious? Can EMA confirm if this is how they will handle R2 to R3 conversion, or will term highlighted be considered?</p>     | <p>The BFC tool follows the published ICH documentation "3_BFC Element Mapping.xlsx". This document states that seriousness at case level is copied to all reactions.</p> <p>You might find the following training modules and workshop recordings useful:</p> <ul style="list-style-type: none"> <li>• <a href="#">PhV-M2a Implementing ISO ICSR/ICH E2B(R3): Key changes for pharmacovigilance</a></li> <li>• <a href="#">PhV-M2b Implementing ISO ICSR/ICH E2B(R3): Backwards and forwards conversion</a></li> <li>• <a href="#">Workshop on the implementation of ISO standard for individual case safety reports (ICSRs)</a></li> </ul> <p>See also question 2.99</p> |

| Ref.                     | Question   | Answer  |
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| 2.87                     | Is XCOMP available for informal E2B(R3) file testing? If yes, why have we not received an R3 acknowledgement for any R3 test files we have submitted to XCOMP?   | <p>XCOMP can process E2B(R3) files.</p> <p>However, if E2B(R3) test files are not correctly formed i.e. contain parsing errors, they may not receive an E2B(R3) acknowledgement back.</p> <p>If E2B(R3) acknowledgments are not received, a service desk request including an example of the test files that has not received an acknowledgment back should be submitted.</p>                 |
| 2.88                     | How long after notifying the EMA Service Desk of system downtime should the back-up process be implemented? Do we need to wait for EMA confirmation?   | <p>Your back-up process should be started as soon as you have a system failure; there is no need to wait for confirmation of reporting an issue on your side.</p> <p>If there is an issue at the level of the EMA, an announcement will be e-mailed to registered user of EudraVigilance.</p>   |
| 2.89<br><b>(Updated)</b> | <p>Should the MAH submit regulatory authority reports they have downloaded and processed back to the EMA?</p> <p>For example if we identified a special situation, such as an off label use for our product, or other adverse reaction not initially coded, we added the coding into our own database.</p> | <p>No, you must NOT resubmit the case to EudraVigilance as there is no new information from the primary source. This would cause case duplication and subsequent new automatic master cases for you to download and process.</p> <p>If you believe information has not been correctly captured for an ICSR please contact the organisation that has submitted the ICSR to EudraVigilance.</p> |

| Ref. | Question   | Answer  |
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| 2.90 | Please confirm if Batch receiver identifier (N.1.3) and Message receiver identifier (N.2.r.1) shall be the same or it can be different? Please further explain any other scenario where both N.1.3 and N.2.r.1 can be different?   | For ICSRs sent to EudraVigilance, N.1.3 and N.2.r.1 must be identical.<br><br>There is no situation for MAHs or sponsors of clinical trials for these fields to be different. |
| 2.91 | Batch Transmission date (N.1.5) is populated automatically in XCOMP. Can you explain the time zone followed? As per EU ICSR IG, it is stated that no date/time value should exceed the current UK GMT time plus 12 hours. Can you explain the validation error it may show in XCOMP? | EVWEB uses UTC time. For the error message, please see business rule 18 in the Excel file " <a href="#">Human Business Rules R3 Detailed V0.98.xls</a> ".                     |
| 2.92 | In EU, which scenarios do fulfil the local criteria (C.1.7) option "No" or "NI".   | There are no scenarios for an ICSR submission in the EU where "No" or "NI" are applicable.  |

| Ref. | Question  | Answer  |
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| 2.93 | As per ICH E2B(R3), the values allowed for the data element "Other Case Identifier" (C.1.9.1) are: "True" and null flavour "NI". In EV XCOMP, the value "No" is also available. In which scenario, the values "No" and the null flavour "NI" shall be selected? | <p>The EudraVigilance system supports the Boolean datatype and the nullflavor; the field should only be completed if the value is "true".</p> <p>However, in order for EudraVigilance to be able to process Boolean values and the nullflavor(s), all values are accepted for this field including "No" and "NI".</p> |
| 2.94 | Is there an option to add and save a filter for active substance?   | The saving of filters is available in the ICSR download section only.   |
| 2.95 | When exactly are ICSR data refreshed for download within EudraVigilance i.e. will this be on a daily basis at a set time each day?  | The data for download are refreshed overnight (UK time) and organisations are able to download ICSRs processed up to the end of the previous day. The date of the last refresh is displayed on the ICSR download page of EVWEB, which is usually updated each morning at 9AM UK time.                                 |
| 2.96 | After reviewing the eRMR and line listings from EVDAS, do we have to use EVWEB to download ICSRs? Is there any other way to execute the download? Where can specific ICSRs be downloaded that are required for further analysis of a potential signal?          | Registered EVDAS users have links available in the line listings to ICSR forms. EVWEB can also be used to retrieve individual cases which can be displayed as ICSR form and also downloaded as E2B(R3) XML files.   |

| Ref.  | Question   | Answer   |
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| 2.97  | If a field is populated with data in an NCA case, but has No ('N') in access for level 2A/2B how will this appear when MAH download the case? Example: if birthdate (D.2.1) is entered in an NCA case, will MAH see this as no value or as MASKED? | There are no data displayed, however for birthdate a calculated age is provided where applicable.  |
| 2.98  | Do re-routed ICSRs have both medicinal product name and substance name included in the XML file?   | If this information is reported in the ICSR, then it appears in the appropriate data element in the rerouted file.   |
| 2.99  | Does EMA monitor MAHs download of level 2B access ICSRs?   | The EMA keeps a log of all L2B download requests.  |
| 2.100 | ICSRs uploaded to EV via the EV-Post function: my understanding is, that ICSRs can be uploaded either in E2B(R2) or to the (R3) format and the download format (from EVDAS or EVWEB) depends from the upload format. Is my understanding correct?  | <p>The EVPOST function can be used to send either R2 or R3 ICSRs.</p> <p>MAHs can only download ICSRs from EV in E2B(R3) format. ICSRs are rerouted to NCAs in the format as received by EudraVigilance.</p> <p>Access to data via EVWEB or EVDAS is provided in E2B(R3) format for NCAs and MAHs.</p> |

| Ref.  | Question  | Answer  |
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| 2.101 | <p>What happens if different stakeholders using different E2B standards are involved in the same case? As far as we know, the "once R3, always R3"-rule applies, e.g. an authority submits a case using the E2B(R3) standard to EudraVigilance. Later on, an MAH gets follow-up information regarding this case. How can MAHs communicate this information?</p> | <p>This rule applies to the sending organisation only. Different senders can use either of the E2B ICSR formats for cases with the same WWID. If there are different senders, then these are considered as different cases in EV and the duplicate management process in EV then creates an E2B(R3) version of such transmissions.</p>  |
| 2.102 | <p>Does EMA re-route copies of literature articles after 22 Nov 2017, which it received by e-mail (<a href="mailto:EVLIT@ema.europa.eu">EVLIT@ema.europa.eu</a>) if the MAH has sent the ICSR in R2 format?</p>   | <p>If an article is attached to an E2B(R3) ICSR, it is included in the rerouted file.</p> <p>If an MAH is using E2B(R2) and sends the article to <a href="mailto:EVLIT@ema.europa.eu">EVLIT@ema.europa.eu</a>, then the article is linked to the case in ETL (assuming they correctly used the case number as the file name of the article) &amp; then NCAs will be able to access the article through EVWEB.</p> |

| Ref.  | Question  | Answer   |
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| 2.103 | Can you further describe the duplicate management process applied by EMA? | <p>The duplicate management process applied by EMA is as follows:</p> <ul style="list-style-type: none"> <li>• When EMA identifies and confirms that two cases are duplicates, a master case is created.</li> <li>• The underlying duplicates are retained, but their status is changed so that they are excluded from signal detection.</li> <li>• If an NCA has selected to receive master cases, then they are rerouted in the same way as the duplicates were rerouted previously.</li> <li>• MAHs receive master cases as part of the EV download functionality.</li> <li>• Organisations then have to manage the master cases and duplicates in their local pharmacovigilance systems. The process for managing duplicates in local pharmacovigilance systems must not trigger any resubmission of ICSRs to EV except upon receipt of new information relevant to the case, which then should be handled as follow-up.</li> <li>• If a follow-up is submitted by an organisation related to a master case created in EV, EMA updates the master case based on the follow-up information received. The updated master case based on the new information is then either rerouted to the corresponding NCA or made available to MAHs via the EV download functionality, as applicable.</li> </ul> |

| Ref.  | Question   | Answer  |
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| 2.104 | <p>In the instance reference file '00_EU_ICSR_Reference_Instance_v3_6', the codes for elements D.1.1.1 to D.1.1.4 (Patient medical record number(s) and source(s) of the record number) have specific numeric values (i.e. code="1" for D.1.1.1). In the ICH E2B(R3) ICSR Implementation Guide indicates that specific character values must be used (i.e. code="gpmrn" for D.1.1.1). Could you clarify which codes must be used for these elements?</p> | <p>The code values to be used are published in the ICH E2B(R3) code list file: "CL4_ich-medical-record-number-source-type.gc.xml". This is available as part of the ICH download package folder "7_E2B Bilingual Code Lists".</p> <p>There is no difference between the EU reference instance and the ICH reference instance for this field.</p> <p>The <a href="#">ICH E2B(R3) Implementation Guide</a> includes XML snippets that were created before the reference instance and final code lists were available and published and will need to be updated.</p> |

| Ref.  | Question  | Answer   |
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| 2.105 | <p>In instance reference file '00_EU_ICSR_Reference_Instance_v3_6', the code systems for several elements as G.k.2.1.1b, G.k.2.1.2b, G.k.2.3.r.2b are prefixed with 'TBD-' (i.e.: <code>&lt;code code="G.k.2.1.2b" codeSystem="TBD-PhPID" codeSystemVersion="G.k.2.1.2a"/&gt;</code>). Can you confirm that TBD stands for 'To be defined', and the correct codeSystem are the ones in the instance reference file without 'TBD-' implemented ?</p> | <p>TBD does stand for "To be defined".</p> <p>As the ISO IDMP standard is not yet ready for implementation, there is no published OID codesystem to be included in the reference instance.</p> |

| Ref.  | Question   | Answer   |
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| 2.106 | <p>When converting an E2B(R3) file using the BFC tool, the seriousness criteria are systematically set to '1' in E2B(R2) when the value was originally set to 'true'. But according to the ICH ICSR BFC specifications, the conversion logic for seriousness criteria must consider the value of the element E.i.3.1 (Term highlighted by reporter). Could you clarify, if seriousness criteria should be set to '1' in R2 after conversion when the criteria was set to 'true' in R3, or only if the element E.i.3.1 has the value '3' (Yes, highlighted by the reporter, SERIOUS) or '4' (No, not highlighted by the reporter, SERIOUS) for this criteria?</p> | <p>The ICH BFC rules state the following:<br/> The E2B(R2) field A.1.5.1 should be set to 'Yes' if there is at least one reaction/event with the corresponding seriousness criteria set to 'true' (i.e., E2B(R3) field E.i.3.2).<br/> Each seriousness criteria (i.e., E2B(R2) fields A.1.5.2) should be set to 'Yes' if there is at least one reaction/event, highlighted as serious, with the corresponding criteria set to 'true' (i.e., E2B(R3) field E.i.3.2).</p> <p>Example:</p> <p>Input in E2B(R3):</p> <ul style="list-style-type: none"> <li>• Reaction 1: <ul style="list-style-type: none"> <li>○ Term highlighted by reporter (E.i.3.1): yes, serious</li> <li>○ Seriousness criteria (E.i.3.2): death: yes; disabling: no</li> </ul> </li> <li>• Reaction 2: <ul style="list-style-type: none"> <li>○ Term highlighted by reporter (E.i.3.1): no, serious</li> <li>○ Seriousness criteria (E.i.3.2): death: no; disabling: yes</li> </ul> </li> </ul> <p>Output in E2B(R2):</p> <ul style="list-style-type: none"> <li>• Serious (A.1.5.1): yes</li> <li>• Seriousness criteria (A.1.5.2): death: yes; disabling: yes</li> <li>• Reaction 1 (B.2.i.3): Yes, highlighted, serious</li> <li>• Reaction 2 (B.2.i.3): No, not highlighted, serious <ul style="list-style-type: none"> <li>○ Term highlighted by reporter (E.i.3.1) is not used in this calculation of A.1.5.2 fields</li> </ul> </li> </ul> |

| Ref.  | Question   | Answer   |
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| 2.107 | In a E2B(R3) file, when the element C.1.6.1 (Are Additional Documents Available?) has the value 'false', the corresponding R2 element A.1.8 has the value '1' after conversion by the BFC tool. Actually, the BFC tool systematically sets the element A.1.8.1 with the value '1' regardless of the value of C.1.6.1 in E2B(R3). Can you clarify if there is an issue with the BFC or if this is the expected behaviour? | The BFC tool adds the following text in the additional documents section for E2B(R2) files are converted from an E2B(R3) original file: "Source of this Case Safety Report in E2B(R3) Format:" therefore A.1.8.1 has the value "1" for all converted ICSRs.  |
| 2.108 | Is there another role for the "Medically Confirmed" field besides just to confirm if the case has been medically confirmed by HCP?   | <p>The full name of the "Medically Confirmed?" flag (ICH E2B(R2) A.1.14/ICH E2B(R3) E.i.8) is "Was the case medically confirmed, if not initially from a health professional?".</p> <p>It is for use when version 0 was reported by a consumer or other non-HCP and follow-up has been obtained from an HCP, who has seen the patient.</p> <p>For details please refer to the ICH ICSR Implementation Guide.</p>   |
| 2.109 | Sender's Diagnosis field - What information should be provided in this field?  | <p>The "Sender's diagnosis" field should be used to provide the diagnosis of the sender (i.e. the MAH/NCA). This is only really relevant when a number of reactions have been reported and you, the sender, think that they are symptoms of a particular syndrome.</p> <p>For example if a consumer reports excessive thirst, excessive hunger, blurred vision, fatigue and excessive micturition and the MAH thinks that this is probably early signs of diabetes, then you would code each of the terms separately in the reaction section and then add diabetes in the senders diagnosis.</p> |

| Ref.  | Question  | Answer   |
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| 2.110 | Is the use of field B.4.k.19 'Additional information on drug' to specify any additional information pertinent to the case mandatory? If yes, what information should be provided in this field? | No, it is not mandatory.<br><br>If you have any information on the drug which cannot be coded in the structured fields or the dosage free text field, but is clearly related to the drug, then you would enter it there.<br><br>For example you might enter "started drug over 10 years ago" if that's all you know about the time to onset. |
| 2.111 | For case narrative exceeding 20,000 characters (in R2, 100,000 in R3). How should the exceeding narrative be reported?  | The additional narrative should be stored as a pdf file and either emailed to <a href="mailto:evlit@ema.europa.eu">evlit@ema.europa.eu</a> if you are transmitting in R2 format or attached to the case if you are transmitting in R3 format.  |
| 2.112 | Can we multiple countries be selected while downloading ICSR from EVWEB?  | The country filter in the ICSR download section has been extended to support the selection of more than one country (please refer to the EVWEB release notes). The use of the country filter is not required. If no country is selected the requesting organisation will retrieve all EEA ICSRs.   |
| 2.113 | Please can you confirm the email address that is used by the EMA to confirm duplicates with the MAH, or request additional information?   | The EMA writes to the QPPV and the functional email address as registered in the EV registration database. The EMA does not maintain any additional MAH email addresses for the duplicate management purpose.  |

| Ref.  | Question  | Answer   |
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| 2.114 | <p>What is the mandatory switch from E2B(R2) to (R3)?</p> <p>We understand that it will be upon ISO IDMP implementation, but what stage of implementation? Following any of the IDMP project iterations implementation or at the go-live probably in 2019/2020?</p>                 | <p>There is, at present, no deadline agreed. This is planned to be further discussed with the EU Regulatory Network in 2018.</p>   |
| 2.115 | <p>We (an MAH) have often noticed that cases received from NCAs have ADRs coded that do not match with the ADR descriptions in the verbatim (for example, "edema lip" is frequently coded with the MedDRA term "edema").</p> <p>What is an MAH is expected to do in such cases?</p> | <p>It is for the MAH to determine how to process data downloaded from EudraVigilance according to their SOPs. However, ICSRs downloaded from EudraVigilance should not be resent to EudraVigilance if there is no new information. Details are provided in <a href="#">GVP Module VI</a></p> |

| Ref.  | Question   | Answer  |
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| 2.116 | <p>Does EMA have any expectation from MAHs related to the import of ICSRs downloaded from EudraVigilance into their Safety Databases? In particular, should an MAH import into the Safety Database every downloaded ICSR and then perform case exclusion (e.g. for brand name, pharmaceutical form etc.) within the database or would it be possible for MAHs to perform case exclusion before importing them into the database?</p> | <p>The case review for inclusion or exclusion should be performed in accordance with <a href="#">GVP Module VI</a> as regards the pharmacovigilance responsibilities in the EEA. The outcome of the review should be documented in accordance with the SOPs as part of their overall pharmacovigilance system of the MAH.</p> <p>For the technical implementation of the documentation of the outcome of the review, it is for the MAH to determine the best approach.</p>                                |
| 2.117 | <p>Is the MAHs' access to EudraVigilance for ICSR downloading monitored and tracked by EMA and/or NCAs for compliance purposes? For example, for the planning of PhV inspections?</p> <p>Alternatively, should an MAH implement internal procedures and tools to be able to show to PhV inspectors that the screening of EudraVigilance is performed with a defined periodicity?</p>   | <p>The pharmacovigilance responsibilities for the MAH are set out in Regulation (EC) 726/2004 and Directive 2001/83/EC and further specified in the Commission Implementing Regulation (EU) 520/2012 as well as GVP Module VI and GVP Module IX.</p> <p>In accordance with the provision set out above, the MAH should define the frequency of the ICSR download and the further processing of the downloaded ICSRs as part of their SOPs, which form part of their overall pharmacovigilance system.</p> |

| Ref.  | Question   | Answer  |
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| 2.118 | <p>In EU Individual Case Safety Report (ISCR) Implementation Guide, section "What to do in case of system failure": (EMA/51938/2013 Rev. 1, 06 Jul 2017) section I.C.2.1.6.2 Failure of message transmission by the sender Gateway, it is mentioned that Eudralink can be used to submit ICSRs (instead of using a CD-ROM).</p> <p>In which format (XML, Excel, CIOMS, PDF) should the attachments be provided?</p> <p>How many ICSRs should be provided per file attached?</p> <p>To which EMA email address should those ICSRs (in case of transmission issue at MAH gateway) be sent?</p> | <p>Only valid E2B(R2) or E2B(R3) XML files can be used as an option in case of a failure of a sender's system. As per standard practice, there can be no more than 100 ICSRs per file, and the EMA recommends a maximum of 50 ICSRs per file.</p> <p>If an organisation has a system failure, they should contact the EMA service desk to report the failure and provide details on the back up process they will be following.</p> <p>If EudraLink is being used to send XML files, the service desk will provide an e-mail address to be use for the sending of the XML files upon request at the time of the system failure.</p> |

| Ref.  | Question   | Answer  |
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| 2.119 | Files downloaded from EudraVigilance may contain reactions/events reported in languages other than English in E.i.1.1a. If E.i.1.1a is populated the native language will be provided in E.i.1.1b. For events reported by the primary source in English language are the reactions reported in the EudraVigilance download files in E.i.1.2? | The ICSRs are provided as reported to EudraVigilance, suspected adverse reactions are coded against MedDRA.<br><br>For reports submitted in English the field E.i.1.2 should be populated in English. |
| 2.120 | When organisations are importing ICSRs from EVWEB in E2B(R3) format, then in what format should ACKs be sent: R3 only or is R2 acceptable?   | MAHs <b>must not</b> send ACKs for ICSRs downloaded from EudraVigilance. Please refer to the <a href="#">EU ICSR Implementation Guide</a> and the training videos that have been created.             |
| 2.121 | Are nullification reports included as part of the EVWEB download functionality?  | Nullification reports are included for download from EVWEB.   |

| Ref.  | Question  | Answer  |
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| 2.122 | <p data-bbox="331 252 748 363">With the new upcoming- WHO Drug Dictionary format changes from B2/C2 to B3/C3:</p> <p data-bbox="331 387 748 499">a. When does EMA implement the new dictionary format in their system?</p> <p data-bbox="331 523 748 699">b. What is the impact on the organisations who are downloading ICSRs from EVWEB and converting them into E2B(R2) format?</p> <p data-bbox="331 722 748 836">Would these conversion tools be able to handle the new dictionary format?</p> | <p data-bbox="770 252 2060 363">a. EudraVigilance uses the data from the Art57 (XEVMPPD) database, not the WHO dictionary. For details on the implementation on the ISO IDMP set of standards please consult <a href="#">this page</a> on the EMA website.</p> <p data-bbox="770 387 2060 459">b. The E2B(R3) file contains drug names in free text. The BFC tool copies this free text to the corresponding E2B(R2) free text field.</p> |

| Ref.  | Question   | Answer  |
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| 2.123 | <p>Should MAHs resubmit ICSRs accessed through the EVWEB download functionality that are actually NCA cases?</p> <p>NCA's have observed that some MAHs submit their own version of the NCA case (maintaining the NCA Worldwide Case ID), without having received additional new information. Sometimes MAHs they upgrade the seriousness (from non-serious to serious) and create their own version of the case narrative.</p> | <p>MAHs should not resubmit ICSRs to EudraVigilance, which have been downloaded by means of the EVWEB download functionality, except new information is obtained by the MAH in the context of follow-up as outlined in GVP Module VI.</p> <p>Note: If MAHs submit an updated version of the ICSRs originating from NCA's to EV, they are replacing the previous version of the ICSR in the respective NCA database. The EMA auto-duplicate-master tool also creates a new version of the ICSR (with the World-wide Case Identifier used by the NCA). The respective NCA is therefore receiving 2 new versions (an MAH version and an Auto-Master version) of their own case without any additional value.</p> |
| 2.124 | <p>Please confirm if a signed hardcopy of the confidentiality agreement is also required to be provided to EMA (EV Access Policy, annex c) or whether the confidentiality undertaking is only required electronically in EVWEB (per recent Q&amp;A on EV)?</p>   | <p>A signed hardcopy of the confidentiality agreement is not needed. The confidentiality agreement is provided via the EVWEB interface. For the L2B download, confirming agreement with the confidentiality undertaking by means of a tick box is the process to be followed. The EMA is tracking L2B download requests.</p>  |

| Ref.  | Question   | Answer   |
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| 2.125 | <p>Could you please provide a description/impact about the "clean-up" of the cases available for the download? On which day do you recommend to perform the download?</p>  | <p>The date for ICSR downloads is based on the date the ICSR last had one of the drugs classified against the art57 XEVMPD data.</p> <p>An ICSR can have many suspect drugs and classification against product data may occur several times for the same ICSR over several days. The reason for using classification date for ICSR downloads is that an MAH that previously did not have L2A access may get access on a later date to the receipt of the information.</p> <p>Most classifications happen immediately upon receipt (95-99%) and the rest are manually classified in the week after receipt of the ICSR by EudraVigilance. Therefore a percentage of ICSRs may reappear if a daily approach to downloading ICSRs is taken by an MAH.</p> <p>It is therefore recommend that MAHs set the end date of the L2A downloads to at least 3 days before the last available date indicated on screen in order to reduce the number of times an ICSR could be downloaded</p> |
| 2.126 | <p>When searching under ICSRs, it is not possible to search by transmission date for non MLM cases. Is it normal that cases originating from other senders than the MLM Service do not have a transmission date, please could you help us understand this?</p> | <p>Do not search by transmission date for non-MLM ICSRs. This date is populated by the sender organisation and may not always be reliable. Indeed, it is best to only use the ICSR download section, not the ICSR section for obtaining and downloading the cases that you need.</p> <p>The ICSR section has restrictions to data fields that the ICSR Download section does not, so you will see differences like this. The differences in the levels of access to the data fields is explained in the EV access policy</p>   |

| Ref.  | Question  | Answer  |
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| 2.127 | <p>Why do we see follow up information from laboratories whereas we don't have to re-send serious case received from NCA/EMA? In fact this can be confusing since it was not real follow up information but just the initial report manages by the laboratory, with its own convention.</p> | <p>That is because some MAHs do not follow the rules of how to manage cases and not to retransmit them. EMA will be contacting all such MAHs. However, EMA will need to review this on a case by cases basis.</p> <p>Based on examples you have experienced, please inform the Service Desk and indicate the world-wide unique case numbers or local report numbers for these ICSRs. EMA will contact those MAHs to inform them to cease these erroneous retransmissions.</p> |

| Ref.  | Question  | Answer   |
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| 2.128 | <p>If a patient is treated within a compassionate use program with a non-approved medicinal product and adverse reactions are reported (per legislation) directly to the local health authority and not to the company by the prescribing physician, then it seems that we might not be able to download these cases from EudraVigilance because we would not have an entry in XEVMPD for the product prior to approval neither as clinical study sponsor, and so cases would not be available to us for download.</p> <p>Moreover the level 1 access (ADRreports) does not permit to identify single cases which might relate to the compassionate use programme.</p> <p>In this situation, how can the company managing the compassionate use retrieve those cases from Eudravigilance?</p> | <p>When a medicinal product not authorised in the EEA is supplied under compassionate use or named patient use, access to the detailed information of ICSRs (Level 2A or Level 2B) submitted to EudraVigilance by NCAs should be requested by the organisation (Sponsor, applicant, marketing authorisation holder, hospital or wholesaler) supplying the product directly to the concerned NCA of the Member State where the compassionate use is authorised.</p> |

| Ref.  | Question  | Answer  |
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| 2.129 | <p>When an ICSR is received with a suspected drug owned by the MAH but the reaction has not a compatible onset time or there are mistakes in the coding. Could companies modify or discard this ICSR before entering it into the MAH database? Should MAHs inform the EMA of these detected errors? In case yes, how MAH should inform the EMA?</p> | <p>You should not normally modify data received via your L2A Downloads. If the original MAH made a mistake in the coding, then you should contact them directly.</p> <p>If it is a mistake that calls into question the validity of the case or ADR, then you may wish to wait for confirmation of case validity before entering it into your own database.</p> |
| 2.130 | <p>I have identified in EVDAS ICSRs that have been submitted to EV by other MAHs. The receipt date of these ICSRs is older than the go-live of the new EVWEB system including the L2A download functionality, therefore not available to us for downloading. Am I obliged to process these ICSRs in my safety database?</p>                         | <p>No you are not obliged to process them in your database. You should have received such cases from the concerned NCA when they were transmitted if you had an obligation to process them.</p>   |

| Ref.                  | Question   | Answer  |
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| 2.131<br><b>(new)</b> | If we download an ICSR from EVWEB and find something in medical history of the download which leads MAH to create another ICSR from the medical history product/ event, should that ICSR be transmitted to EMA if it meets reporting criteria? | <p>EMA has recently published a new note for clarification on the recording by marketing authorisation holders of information on suspected adverse reactions held in EudraVigilance.</p> <p>This document provides guidance on the obligations of MAHs to record information on suspected adverse reactions they access in EudraVigilance, taking into consideration their pharmacovigilance obligations in the EEA in the context of the pharmaceutical legislation for medicinal products for human use.</p> <ul style="list-style-type: none"> <li>➤ The document is accessible directly via the following link:<br/><a href="http://www.ema.europa.eu/docs/en_GB/document_library/Other/2018/07/WC500252292.pdf">http://www.ema.europa.eu/docs/en_GB/document_library/Other/2018/07/WC500252292.pdf</a></li> <li>➤ It is published on EMA website under the page 'Access to EudraVigilance data' linked hereafter, in the section Stakeholder groups: Marketing authorisation holders (see highlight in screenshot below).<br/><a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000674.jsp&amp;mid=WC0b01ac0580a69390">http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000674.jsp&amp;mid=WC0b01ac0580a69390</a></li> </ul> |
| 2.132<br><b>(new)</b> | We have downloaded some mastercases in which the case first sender is stated as Regulator, however there is not any NCA case number neither in WW case ID nor duplicate in case number field. Can we assume that these cases are not from NCA? | All Master cases are transmitted to EVHUMAN or EVCTMPROD by the sender identifier EVHUMANWT. That is an affiliate of EV and, as such, is registered as an NCA. Therefore all master cases will appear to be NCA cases. The field "Source(s) of the Case Identifier" (ICH E2B (R3) C.1.9.1.r.1) will provide the sender identifier of each case. That will tell you whether they are MAH or NCA cases. If they are all MAH cases, then you should treat the master as though it were an MAH case.  |

| Ref.                  | Question   | Answer  |
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| 2.133<br><b>(new)</b> | Do MAHs need to send cases with a co-suspect related to another company's product to that other company (when there is no LP agreement), if the case (events) took place in the EU? Can we expect that if that company is an MAH in the EU it is their responsibility to download cases related to a product that can't be excluded as theirs and therefore we would no longer have an obligation to send them the report that has their product as a co-suspect?" | <p>If you send the cases to the other MAH as well as to EV, then they will have an obligation to process them and transmit them to EV too. The EMA will then have to merge the duplicate cases under a master. You will download both the other MAH's case &amp; the master, the other MAH will download your case and the master &amp; every other MAH will download all 3 cases. For all organisations, 1 case will become 3.</p> <p>Conversely, if you do NOT send it to the other MAH &amp; simply transmit your case to EV, then you will have fulfilled your reporting obligations and they will be able to download it from EV as necessary so that they can fulfil their obligations too.</p> |

### 3. Medical Literature Monitoring

From version 1.7 of the Q&A document, the MLM questions will be migrated to the [MLM Q&A document](#) and maintained there.

### 4. Guideline on good pharmacovigilance practices: Module VI – Management and reporting of adverse reactions to medicinal products

| Ref. | Question   | Answer   |
|------|--|--|
| 4.1  | Should literature articles always be provided with a case, or is this only on request? | <p>Copies of literature articles do not need to be routinely submitted. A copy of the article should only be submitted upon request as stated in GVP Module VI, Chapter VI.C.6.2.3.2 Suspected adverse reaction reports published in scientific literature:</p> <p>"Upon request of the Agency, for specific safety review, a full translation in English and a copy of the relevant literature article shall be provided by the marketing authorisation holder that transmitted the initial report, taking into account copyright restrictions [IR 28(3)]".</p> |

| Ref. | Question  | Answer   |
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| 4.2  | Can an initial report be submitted as an amendment e.g. if a case is classified as 'invalid and not submitted, but on further review found to be valid (with no new information received) could this be submitted as an amendment or would it be a late case? | <p>Amendment reports apply to valid ICSRs which have already been submitted to EudraVigilance. In this example the report was initially considered non-valid and upon further review found to be valid (with no new information received).</p> <p>The valid ICSR should be submitted as initial report. The clock for the submission starts as soon as the information containing the minimum criteria has been brought to the attention of the organisation; i.e., when the case was initially received.</p> <p>For further reference, GVP Module VI Chapter VI.B.7, Submission of individual case safety reports (ICSRs) states the following:</p> <p>"The clock for the submission of a valid ICSR starts as soon as the information containing the minimum criteria has been brought to the attention of the national or regional pharmacovigilance centre of a competent authority or of any personnel of the marketing authorisation holder, including medical representatives and contractors. This date should be considered as day zero."</p> |
| 4.3  | If a follow-up is required by an MAH on a case that was submitted to EudraVigilance by an NCA, does the MAH follow-up directly with the NCA or with EudraVigilance?   | <p>GVP Module VI Rev 2 Chapter VI.C.2.2. Responsibilities of marketing authorisation holder in EU states the following:</p> <p>"For ICSRs made accessible to marketing authorisation holders from the EudraVigilance database in accordance with REG Art 24(2) and in line with the EudraVigilance access policy, the routine request for follow-up by the marketing authorisation holders is not foreseen. If the follow-up of an ICSR is necessary for a specific situation, a justification should be provided with the request, which should be addressed directly to the sender organisation of the ICSR."</p>  |
| 4.4  | With the introduction of null flavour data elements in ICH E2B(R3), what is the Agency's expectation on submitting follow-up report when the follow-up query is sent after initial report submission?   | <p>The batch number for biological medicinal products is one of the main data elements, where the outcome of the follow-up is important to be notified.</p> <p>For example, an ICSR should be submitted as amendment report to EudraVigilance with the applicable null flavour (ASKU) where the information (e.g. batch number of a vaccine) was asked for but the primary source did not respond to the request for information.</p> <p>Where the information (e.g. batch number of a vaccine) is asked for and is provided by the primary source, a follow-up should be submitted to EudraVigilance based on this new information. Where the primary</p>   |

| Ref. | Question  | Answer  |
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|      | <p>For example, if a report was initially submitted with a null flavour data element response of UNK, NI or NASK (per company default) then MAH updates the responses to ASKU after the follow-up query is sent. Is there an expectation for the MAH to submit follow-up reports to indicate all these null flavour field responses have now been changed to ASKU? Would this follow-up submission be considered "Amendment"?</p> | <p>source confirms that the information is not available, the applicable nullflavor (ASKU) is also to be submitted as follow-up.</p> <p>For reference please also see GVP Module VI Rev 2 App VI.1.2: Follow-up of ICSRs by competent authorities in Member States with involvement of marketing authorisation holders. Step 11.2: MAH to "Inform NCA that it was not possible to obtain follow-up information."</p> <p>And GVP VI Rev 2 Chapter VI.B.7.3, Amendment report:</p> <p>"There may be instances, where a valid report which has already been submitted may need to be amended for example when, after an internal review or according to an expert opinion some items have been corrected, (such as adverse event/reaction terms, seriousness, seriousness criteria or causality assessment) but without receipt of new information that would warrant submission of a follow-up report. (...) These submissions are considered as amendment reports."</p> <p>For further information on the use of nullflavor refer to the EU ICSR Implementation Guide (chapter I.C.3.7 Usage of nullflavor flags).</p> <p>If follow-up cannot be made UNK will be appropriate.</p> <p>NASK can be used if no attempt at follow-up has been made.</p> |
| 4.5  | <p>If we do not have permission to follow up, which null flavour should be used? Where FU is received and a null favour is updated to actual new information, is this the only time you would expect a FU report to be submitted? Or should this be done regardless of what the null flavour field is updated to e.g. No Information?</p>   | <p>The ICSR should be created or updated in accordance with the data that has been initially provided and received. See question 4.4.</p> <p>No permission to F-UP, UNK ("A proper value is applicable, but not known"), or NI ("No information whatsoever can be inferred from this exceptional value") are example of nullflavors that may be used.</p> <p>From GVP Module VI Chapter VI.C.6.2.2.7. Follow-up information:</p> <p>"NCAs and MAHs "should submit follow-up ICSRs if significant new medical information has been received. Significant new information relates to, for example, a new suspected adverse reaction, a change in the causality assessment, and any new or updated information on a case that impacts on its medical interpretation. Therefore, the identification of significant new information requiring to be submitted always</p>   |

| Ref. | Question   | Answer  |
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|      |  | <p>necessitates medical judgement. (...)"</p> <p>For further details see also question 4.4.</p> |
| 4.6  | <p>What are the reporting and download rules of ICSRs after go-live of the new EV system for the below scenario?</p> | <p>Please refer to the answers as provided below:</p>   |

**Figure 1.** Response to question ID 4.6

|    | <b>Scenarios</b>  | <b>ICSR reporting before 22 November 2017</b>  | <b>Simplified reporting – post 22 November 2017</b>  | <b>EVWEB ICSR download</b>   |
|----|---|--|--|--|
| a) | Both companies have marketing authorisations in the EU and each handles their reporting.  | Both partners report to the individual countries in the EU where they are the MAH;<br><br>Scenarios for reporting to EudraVigilance:<br><br>Partners both report to EudraVigilance for countries outside the EU or<br><br>Partner reports to EudraVigilance in countries outside EU on behalf of the other company | Is it OK for both partners to report to EudraVigilance or should one company do this on behalf of the other? (Or is either OK?)<br><br><b>Answer</b> - The partnership agreement should clearly define which party performs reporting to EudraVigilance. This should also be clearly documented in the pharmacovigilance system master files (PSMF) of both parties.<br><br>In such situations where an agreement is in place one party can perform the reporting.<br><br>If no agreement is in place both parties can report. However it is strongly encouraged that the same worldwide unique case identifier is used. | Should one partner download (helps avoid duplication) or should both companies download?<br><br><b>Answer</b> - For downloading of data from EudraVigilance it is up to each organisation how they wish to organise themselves for reporting obligations outside the EU and for performing data analysis.<br><br>However, it should be noted that ICSRs submitted by one party will form part of the downloads made by the other company as the ICSR export only excludes ICSRs made by the same headquarter sender. |
| b) | Both companies have marketing authorisations in in the EU but market in different Member States and one partner reports on behalf of the other. | One company reports all cases on behalf of the other   | Can the partner continue to report on behalf of the organisation?<br><br><b>Answer</b> - See above for scenario a)   | As above<br><br><b>Answer</b> - See above for scenario a)  |

|    | <b>Scenarios</b>  | <b>ICSR reporting before 22 November 2017</b> | <b>Simplified reporting – post 22 November 2017</b>   | <b>EVWEB ICSR download</b>  |
|----|---|---|---|---|
| c) | One company reports on behalf of the partner which holds a EU marketing authorisation; note the company is not an MAH in any EU country | The company reports on behalf of the partner. | <p>Can the organisation continue to report on behalf of the partner?</p> <p><b>Answer</b> – From a technical point it is recommended to establish a virtual affiliate under the MAH so that all the cases can be submitted by the other party under the MAH's Headquarter ID.</p> <p>If this is not followed, the ICSRs will appear for EudraVigilance download by the MAH when they perform an export.</p> | <p>Partner, as the MAH, to access and download the ICSRs, or can we do that for them through delegation?</p> <p><b>Answer</b> - Only the MAH has access to the data. Another party would only have access if the MAH gives a user from the other party access to EudraVigilance, this would give the user access to all the MAH's ICSRs for all their products.</p> |

| Ref. | Question  | Answer   |
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| 4.7  | Does the EMA require a deletion notification for an ICSR originally reported to an NCA only prior to 22 Nov 2017 if it is determined after 22 Nov 2017 that a deletion is required?   | Nullifications for ICSRs that were previously sent to NCAs should be submitted to EudraVigilance after 22 November   |
| 4.8  | What is the expectation of the EMA for an ICSR originally reported to an NCA only prior to 22 Nov 2017 and downgraded due to follow-up information received to no longer require submission "by itself" after 22 Nov 2017?<br><br>Should such downgrades be directed to EMA after 22 November 2017?                       | Follow ups that need to be submitted in accordance with the requirements specified in GVP module VI should be submitted to EudraVigilance after 22 November. This includes nullifications (see question 4.7)   |
| 4.9  | We understand that cases exported from EV will not have narratives.<br><br>When we need to report these cases outside of Europe, is it expected that we write our own narrative for the cases, or is it acceptable to request the full case narratives (L2B access?) for all cases that we will need to report elsewhere? | Under the conditions of the access policy (Level 2B) requests for the case narrative should only be made for in the context of reviewing a signal.<br><br>The EMA is not in a position to offer advice on non-EEA requirements for creation and provision of case narrative.<br><br>Please note that EU data protection legislation applies to all EEA ICSRs that are being transmitted to organisations located outside of the EEA. |

| Ref. | Question  | Answer   |
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| 4.10 | <p>Regarding Module VI: Amendment is a significant data clean up, with an initial receipt date equal to last significant information.</p> <p>Must amendments be included into compliance metrics as for significant follow ups?</p> | <p>General guidance on report amendment is provided in GVP VI Chapter VI.B.7.3. (Report amendment). Serious and non-serious cases which have already been submitted to EudraVigilance may need to be amended when, after an internal review or according to an expert opinion some items have been corrected, without receipt of new information that would warrant for the submission of a follow-up report.</p> <p>Where the amendment significantly impacts on the medical evaluation of the case, an ICSR should be resubmitted and information on the amendment should be explained in the case narrative.</p> <p>For example, an amendment of the MedDRA coding due to a change in the interpretation of a previously submitted ICSR may constitute a significant change and therefore should be resubmitted as amendment report.</p> <p>Information on compliance monitoring concerning amendment reports is provided in GVP VI chapter VI.C.6.2.2.8 (Amendment of cases):</p> <ul style="list-style-type: none"> <li>• ICSRs submitted in the ICH-E2B(R2) format will appear as "late reports" in the compliance monitoring performed by the Agency if they are submitted beyond the 7, 15 or 90 days submission time frames since the date of receipt of the most recent information should remain unchanged.</li> <li>• ICSRs set as amendment reports in the ICH-E2B(R3) format are not considered in the compliance monitoring performed by the Agency. They will be however monitored as part of the regular review of the ICSRs quality and integrity conducted by the Agency. This is to ensure that they have not been misclassified by the sending organisation as amendment reports instead of follow-up reports which should be taken into account in the compliance monitoring.</li> <li>• For internal purposes, the MAH should have their own procedures.</li> </ul> |

| Ref. | Question  | Answer   |
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| 4.11 | Where are the current guidelines specifying the revised reporting guidelines for MAHs to report ICSRs for serious and non-serious cases to the EMA after November 22nd? | <p>Information is already provided in chapter VI.C.4 of GVP VI Rev 1.:</p> <p>Once the functionalities of the EudraVigilance database specified in Article 24(2) of Regulation (EC) No 726/2004 are established, the following requirements, detailed in Articles 107(3) and 107a (4) of Directive 2001/83/EC, shall apply within 6 months of the announcement by the Agency to valid unsolicited and solicited ICSRs reported by healthcare professionals and non-healthcare professionals.</p> <p>This is independent of the condition of use of the suspected medicinal product and of the expectedness of the adverse reaction.</p> <p><u>a. Serious ICSRs</u></p> <ul style="list-style-type: none"> <li>Marketing authorisation holders shall submit all serious ICSRs that occur within or outside the EU, including those received from competent authorities outside the EU, to the EudraVigilance database only.</li> <li>Competent authorities in Member States shall submit to the EudraVigilance database all serious ICSRs that occur in their territory and that are directly reported to them.</li> </ul> <p><u>b. Non-Serious ICSRs</u></p> <ul style="list-style-type: none"> <li>Marketing authorisation holders shall submit all non-serious ICSRs that occur in the EU to the EudraVigilance database only.</li> <li>Competent authorities in Member States shall submit all non-serious ICSRs that occur in their territory to the EudraVigilance database.</li> </ul> |

| Ref. | Question  | Answer  |
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| 4.12 | <p>When will the Clinical Trial Regulation (EC) 536/2014 and the simplified reporting of SUSARs directly to EVCTM be implemented?</p>   | <p>Although the Clinical Trial Regulation (EC) 536/2014 was adopted and entered into force in 2014, the timing of its application depends on confirmation of full functionality of the EU clinical trial portal and database through an independent audit.</p> <p>The Regulation will become applicable six months after the European Commission publishes notice of this confirmation.</p> <p>The EMA's Management Board endorsed a delivery timeframe of the EU clinical trial portal and database in December 2015. However, due to technical difficulties with the development of the IT systems, the portal's go-live date has to be postponed.</p> <p>Due to these delays, the EU Clinical Trial Regulation will come into application during 2019 instead of October 2018, as previously scheduled.</p> <p>Information on the Clinical Trial Regulation 536/2014 and its implementation is provided on the <a href="#">EMA website</a></p> |
| 4.13 | <p>In the updated version of Module VI it states "A consumer may provide medical documentations (e.g. laboratory or other test data) that support the occurrence of a suspected adverse reaction and which indicate that an identifiable healthcare professional suspects a causal relationship between a medicinal product and the reported adverse reaction."</p> <p>The previous Module VI wording was "or". Is this a change in the requirements?</p> | <p>Reference is made to GVP VI chapters VI.A.1.5. (Medical confirmation).</p> <p>The update clarifies that a report of suspected adverse reaction submitted by a consumer with supporting medical documentation is considered medically confirmed when it is indicated in the documentation that an identifiable healthcare professional suspects a causal relationship between a medicinal product and the reported adverse reaction.</p> <p>For example abnormal laboratory results submitted without confirmation by a healthcare professional of a causal relationship between a medicinal product and the reported adverse reaction are not considered medically confirmed.</p>  |

| Ref. | Question  | Answer  |
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| 4.14 | What is the timeline for sending Literature articles or other attachments as amendments upon request?   | <p>Reference is made to GVP VI chapters VI.C.6.2.3.2. (Suspected adverse reaction reports published in the medical literature).</p> <p>In accordance with Article 28 (3) of the Commission Implementing Regulation (EU) No 520/2012, upon request of the Agency, for specific safety review, a full translation in English and a copy of the relevant literature article shall be provided by the marketing authorisation holder that transmitted the initial report, taking into account copyright restrictions.</p> <p>MAHs should endeavour to provide the article within the requested timeframe and inform the requester if delay is envisaged.</p>  |
| 4.15 | Health Authority cases – narrative translation. We understand from the below Q&A that certain NCAs expect MAHs to translate HA cases once they are uploaded in EV. Can you please clarify what is expected related to HA cases? Would the MAH be expected to translate all HA cases? Or will it be a collaboration and only when requested for specific cases? Are MAHs required to do this? For serious and non-serious cases? Further information would be appreciated. | <p>Reference is made to GVP VI chapters VI.C.6.2.2.4. (Case narrative, comments and causality assessment) and VI.C.6.2.2.11. (Handling of languages).</p> <p>In accordance with Article 28 (4) of the Commission Implementing Regulation (EU) No 520/2012, competent authorities in Member States may report case narratives in their official language(s).</p> <p>For those reports, case translations shall be provided by the competent authority having submitted the ICSR, when requested by the Agency or other Member States for the evaluation of potential signals.</p> <p>For suspected adverse reactions originating from outside the EU, English shall be used by MAHs in the ICSRs. This is applicable as well for ICSRs received for competent authorities outside the EU.</p> <p>In accordance with Article 28 (3)(m) of the Commission Implementing Regulation (EU) No 520/2012, a case narrative shall be provided, where possible*, for all cases with the exception of non-serious cases.</p> <p>*'Where possible' is usually understood as meaning having received sufficient information from the primary source to prepare a concise clinical summary of the individual case.</p> |

| Ref. | Question   | Answer  |
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| 4.16 | <p>Outbound cases – to be reported to EV: Regarding outbound for domestic cases and the narrative in local language, will MAHs be expected to translate a full case, including narrative for serious and non-serious in English for every case and submit with the local language verbatim text to EV? Or only if specifically requested by a country, otherwise the English version is sufficient?</p> <p>Will you provide a list of NCAs that have requirements for translation? Are you able to provide some further insights how this process is expected to work?</p> <p>Where, after EV Web downloading of cases, a translation is made how would the translation piece be submitted and added to the existing case?</p> | <p>Reference is made to GVP Module VI chapters VI.C.6.2.2.4. (Case narrative, comments and causality assessment) and VI.C.6.2.2.11. (Handling of languages).</p> <p>In accordance with Article 28 (4) of the Commission Implementing Regulation (EU) No 520/2012, where suspected adverse reactions are reported by the primary source in narrative and textual descriptions in an official language of the Union other than English, the original verbatim text and the summary thereof in English shall be provided by the marketing authorisation holder.</p> <p>In practice, the original verbatim text reported by the primary source in narrative and textual descriptions in an official language of the Union other than English should be included in the ICSR, if it is requested by the Member State where the reaction occurred or by the Agency. MAHs should check locally with the competent authorities in Member States for their specific requirements.</p> <p>The ICSR should be completed and submitted in English if not otherwise requested.</p> <p>In accordance with Article 28 (3)(m) of the Commission Implementing Regulation (EU) No 520/2012, a case narrative shall be provided, where possible, for all cases with the exception of non-serious cases.</p> <p>"Where possible" is usually understood as meaning having received sufficient information from the primary source to prepare a concise clinical summary of the individual case.</p> <p>When requested by a Member State or the Agency, the provision of the original verbatim text in an official language of the Union other than English for the suspected adverse reaction and the additional description of the case should be done in the relevant ICH-E2B data elements and sections (see GVP VI Chapter VI.C.6.2.2.11).</p> <p>After downloading a case from EVWEB (whether L2A, L2B or MLM), you should NOT transmit that case back to EudraVigilance unless you have received information directly from the primary source. If you have obtained the narrative via L2B or MLM downloads and translated it, that is NOT new information and it would NOT qualify for retransmission to EV.</p> |

| Ref. | Question  | Answer   |
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| 4.17 | <p>Are companies expected to collect reports of Off-Label-Use (OLU) without AE when a product is provided off label in the context of Named Patient Programs or free goods provision?</p> <p>If so, this would only be considered in aggregate rather than as single cases for B/R. However, if no additional information is available or obtained other than 'OLU' what value is there in this information alone.</p> <p>Could you please clarify GVP Module VI section b. The off-label use of a medicinal product does not result in patient's harm and occurrence of a suspected adverse reaction [...]</p> | <p>When a medicinal product is administered off-label in the context of named patient use/companionate use, the guidance provided in GVP VI chapters VI.C.1.2.2. should be followed:</p> <ul style="list-style-type: none"> <li>• For compassionate use and named patient use conducted in Member States (or in countries outside the EU) <u>where the active collection of adverse events occurring in these programmes is required</u>, the reports of adverse reactions, suspected to be related to the supplied medicinal product by the primary source or the notified organisation, should be submitted as ICSRs in line with the time frames and modalities provided in chapters VI.C.3. and VI.C.4.. They should be considered as solicited reports.</li> <li>• For compassionate use and named patient use conducted in Member States (or in countries outside the EU) <u>where the active collection of adverse events occurring in these programmes is not required</u>, any notified noxious or unintended response to the supplied medicinal product should be submitted as ICSR in accordance with the time frames and modalities provided in chapters VI.C.3. and VI.C.4.. It should be considered as a spontaneous report of suspected adverse reaction.</li> </ul> <p>When a medicinal product is administered off label in the context of a patient support programme, the guidance provided in GVP VI chapter VI.C.2.2.11.(Reports from patient support programmes and market research programmes) should be followed.</p> <ul style="list-style-type: none"> <li>• Safety reports originating from those programmes should be considered as solicited reports. The marketing authorisation holder should have mechanisms in place to record and document complete and comprehensive case information on solicited adverse events and to evaluate that information, in order to allow the meaningful assessment of individual cases. Reports of adverse reactions, suspected to be related to the supplied medicinal product by the primary source or the notified organisation should be submitted as ICSRs in line with the time frames and modalities provided in chapters VI.C.3. and VI.C.4.. They should be considered as solicited reports (see chapter VI.6.2.3.7 Subsection 1 for guidance on the electronic submission of these ICSRs).</li> </ul> <p>With regard to periodic reporting, clinically important safety information originating in these programmes (named patient use/companionate use or patient support programme) should be summarised in PSUR sub-section "Other therapeutic use of medicinal product" (See GVP VII, Chapter VII.B.5.7.4) and taken into consideration as applicable in PSUR section "Integrated benefit-risk analysis for authorised indications" (See GVP VII chapter VII.B.5.18.).</p> <p>Where the off-label use has been included as an important potential risk in the Risk Management Plan with specific pharmacovigilance activities (see GVP V chapter V.B.5.8. and GVP VI chapter VI.C.2.2.12), the evaluation of the risk of off-label use should be addressed in the PSUR section "Signal and risk evaluation" (See GVP VII chapter VII.B.5.16.) and in PSUR section "Integrated benefit-risk analysis for authorised indications" as applicable (See GVP VII chapter VII.B.5.18.).</p> |

| Ref. | Question  | Answer  |
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| 4.18 | <p>In Appendix VI of GVP VI (Rev 2), it is mentioned that EMA will be reviewing the quality, integrity, use of terminologies and compliance with submission time frames.</p> <p>A draft report summarizing the outcome of the quality review is sent by email to the NCA head of PV dept or the MAH EU QPPV. If corrective action is needed by the sending organization, then comments should be provided to EMA within the requested timeframe.</p> <p>Can EMA elaborate on this process and the types of items they will be looking for?</p> <p>Deadlines expected for corrective action?</p> <p>How frequently will these be provided to NCA/MAH?</p> <p>Are there repercussions to companies found with regular non-compliance?</p> <p>Will this begin upon 11/22 date of EV Go Live?</p> | <p>Reference is made to GVP VI chapters VI.B.5. (Quality management) and VI.C.6.2.4. (Data quality of individual case safety reports transmitted electronically and duplicate management).</p> <p>In accordance with Regulation (EC) No 726/2004, Article 24(3), the Agency operates procedures to ensure the quality and integrity of the information collected in EudraVigilance in collaboration with the EU network. This includes identifying duplicate reports, performing the coding of the reported medicinal products and active substances, and providing feedback on the quality of both ICSRs and medicinal product information sent by NCAs, MAHs and sponsors.</p> <p>With regards to the monitoring of ICSR quality and integrity, a review of the completeness of the relevant data elements with the use of the appropriate controlled vocabularies is performed by the Agency at regular intervals for all organisations submitting ICSRs to the EudraVigilance database in line with the Agency's SOPs. The monitoring of the compliance with the 15 and 90 days submission time frames for ICSRs submitted to EudraVigilance is also performed for all organisations.</p> <p>Parameters upon which the review of organisations may be initiated regarding ICSRs quality and integrity, refer for example to</p> <ul style="list-style-type: none"> <li>• the volume of reports being submitted to the EudraVigilance database;</li> <li>• major changes to pharmacovigilance databases;</li> <li>• quality issues identified as part of the signal management;</li> <li>• requests from pharmacovigilance inspectors; or</li> <li>• the time interval since the last review.</li> </ul> <p>The outcome of the review of the ICSRs quality and integrity is provided to the organisations on the basis of a report, which includes the need for corrective measures where applicable and the time frames for these measures to be applied.</p> <p>The time frames and the method for corrective measures depend on the quality issues identified (e.g. corrections of the MedDRA coding of ICSRs to be performed by means of amendment reports).</p> |

| Ref. | Question  | Answer   |
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| 4.19 | Can the EMA share information on the duplicate searches with MAH? What will it look like and what is expected from MAH? | <p>MAHs are expected to review their databases for duplicate cases. You are not expected to actively review EV, as the EMA is doing this.</p> <p>Once duplicates are confirmed, they will be merged under a master case, which will be transmitted to EV &amp; stakeholders will be able to download these.</p> <p>If you suspect duplicate cases in EV, please use dedicated section of the <a href="#">EMA IT Service Desk</a> in accordance with the process described in GVP Module VI, Addendum 1.</p> <p>Please note: In order to help organisations in using the <a href="#">EMA IT Service Desk</a> correctly the following <a href="#">EudraVigilance Support Guide</a> has been updated and now includes a section on the Duplicates Detection.</p> <p>The EMA will be publishing information on our duplicate detection algorithm is performed in due course.</p> |

| Ref. | Question  | Answer  |
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| 4.20 | <p>Please can you explain how duplicates and Master cases are managed and what is not expected;</p> <p>How infinite loops of sending, updating and re-routing are avoided, especially when updates are circulated, incl. nullifications</p> <p>When and what kinds of updates to master cases are expected (can industry as well as NCAs update master cases?) example: translations of NCA local language text, causality assessments on NCA cases</p> | <p>Once the EMA has confirmed that 2 or more cases are duplicates of one another, and that not all the cases in the cluster are from the same sender, then we will make a master case and transmit that to EudraVigilance.</p> <p>The underlying duplicates remain live for the senders to transmit follow-up information, but are suppressed in pharmacovigilance queries such as the eRMR and line listings.</p> <p>If an MAH or NCA receives follow-up for a case, they should assess whether it is significant, in accordance with GVP Module VI, and then update and transmit the case to EV as necessary.</p> <p>Information that the EMA has merged your case under a master or any information contained in a master does NOT constitute significant follow-up, because the receiver (EV) already knows this, so the information is neither medically relevant nor important for case management.</p> <p>If an MAH or NCA makes changes to a master case that they have received and retransmits this to the EMA, then that will be classified as a different case and will be added to the master, therefore organisations should only update cases (either the underlying duplicates or masters) if they have received significant follow-up information from the original sender of the case or have a translation of the narrative.</p> <p>Nullifications DO count as significant updates and should be performed as usual.</p> |

| Ref.      | Question   | Answer   |                |              |              |              |              |           |               |               |  |  |           |                |                |                |  |
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| 4.21      | Case handling and contents: How can EMA be contacted when duplicates have been identified? And how will the nullification process work in terms of feedback to the MAHs? | <p>In accordance with GVP Module VI, Addendum I, Chapter VI. Add I.3.1. "What to do if possible duplicates in EudraVigilance have been detected", if, when reviewing cases obtained from EudraVigilance, there is a suspicion that two or more cases are duplicates of one another; the reviewer should raise a ticket with dedicated section of <a href="#">EMA IT Service Desk</a> with information on which cases are suspected to be duplicates.</p> <p>The information that the Agency needs is either the case numbers (either Worldwide unique case safety IDs or Safety report IDs) or local report numbers (those starting with EU-EC-) of the suspected duplicates in a cluster.</p> <p>To report suspected duplicates, the Agency encourages that the sender sends each suspected cluster of duplicates as a single row in a table similar to the format below:</p> <table border="1" data-bbox="840 660 2049 793"> <tbody> <tr> <td>Cluster 1</td> <td>EU-EC-123456</td> <td>EU-EC-234567</td> <td>EU-EC-345678</td> <td>EU-EC-456789</td> </tr> <tr> <td>Cluster 2</td> <td>EU-EC-1234567</td> <td>EU-EC-2345678</td> <td></td> <td></td> </tr> <tr> <td>Cluster 3</td> <td>EU-EC-12345678</td> <td>EU-EC-23456789</td> <td>EU-EC-34567890</td> <td></td> </tr> </tbody> </table> <p>The EMA will not be nullifying any cases transmitted to EV as part of the duplicate management process; instead we merge confirmed duplicates under a master case, which contains information on the duplicate case numbers in the report duplicates section.</p> <p>These masters are then made available to organisations as part of the normal download process.</p> <p>The EMA will also, after go-live, be making available an EVDAS query that will tell MAHs which of their cases have been merged under a master case as mentioned in question 12.</p> | Cluster 1      | EU-EC-123456 | EU-EC-234567 | EU-EC-345678 | EU-EC-456789 | Cluster 2 | EU-EC-1234567 | EU-EC-2345678 |  |  | Cluster 3 | EU-EC-12345678 | EU-EC-23456789 | EU-EC-34567890 |  |
| Cluster 1 | EU-EC-123456   | EU-EC-234567   | EU-EC-345678   | EU-EC-456789 |              |              |              |           |               |               |  |  |           |                |                |                |  |
| Cluster 2 | EU-EC-1234567  | EU-EC-2345678  |                |              |              |              |              |           |               |               |  |  |           |                |                |                |  |
| Cluster 3 | EU-EC-12345678   | EU-EC-23456789   | EU-EC-34567890 |              |              |              |              |           |               |               |  |  |           |                |                |                |  |

| Ref. | Question  | Answer   |
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| 4.22 | <p>Are there any potential compliance issues that MAHs need to be made aware of?</p> <p>Risks and limitations related to lack of narrative and patient details for ICSRs downloaded from EVWEB: leaves limited option for duplicate check which lead to risk of duplicates and poor quality of data.</p>  | <p>On 23 July 2018 EMA published guidance to clarify the obligations of marketing authorisation holders to record information on ICSRs they access in Eudravigilance.</p> <p><a href="#">Note for clarification: Recording by marketing authorisation holders of information on suspected adverse reactions held in EudraVigilance</a> for MAHs on the recording of ICSRs accessed in EudraVigilance. It provides clarification on the obligations of MAHs on how to record information on suspected adverse reactions accessed in EV.</p> |
| 4.23 | <p>MAH is applying MedDRA coding flag terms as part of the ADR coding e.g. off label use, medication error, pregnancy etc. This is in line with MSSO points to consider. However, it is our experience that the narrative information often contains information qualifying for such flag codes to be transcribed to the case. Therefore, MAHs will be very much relying on the ADR flag coding to be done by NCAs as the narrative will no longer be available. The presence of the coding of these flags is important to ensure appropriate signal detection. Is there any guidance/training provided to NCAs to ensure this?</p> | <p><a href="#">MedDRA training</a> is offered by the MedDRA MSSO in the EEA.</p> <p>The coding performed by NCAs in ICSRs made available for download from EudraVigilance should in principle not be changed.</p> <p>If the MAH has different coding practices e.g. signs and symptoms instead of diagnosis, the MAH may wish to update the coding according to their own coding principles.</p>   |

| Ref. | Question  | Answer   |
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| 4.24 | <p>As described in GVP VI, where a Member State has more than one NCA responsible, ICSRs are re-routed to all relevant NCAs. Thus do the different NCAs of one Member State have to agree on unique re-routing modalities as serious/non-serious, re-coded/uncoded ICSRs etc. or will it be possible to a single NCA to resign receiving re-routed ICSRs at all whereas the other NCA(s) of the same MS still want to get them.</p> | <p>NCAs in EEA Member States can choose themselves the rerouting rules that they wish EudraVigilance to apply to incoming ICSRs.</p> |

| Ref. | Question  | Answer   |
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| 4.25 | <p>The active substance section will not be recoded/inserted by EV, and an (EMA intern, XEVMPD) pix-code will be used. Thus, in line with analyses of the national databases only product-name-based queries will work, which will presumably lead to incomplete results. The consequence would be, to re-code manually each ICSR version received by EV in accordance to the NCA-own coding catalogue.</p> <p>Is it planned/possible either to provide NCAs with the catalogues the pix code is deriving from, or to receive re-routed ICSRs with automatically filled-in active substance sections (so free text analysis would be possible)?</p> | <p>To use the PIX code implemented in EudraVigilance, NCAs would need to implement a complete copy of the XEVMPD database and keep that data synchronised daily. The functionality of data synchronisation does not currently exist and would therefore need to be developed.</p> <p>The XEVMPD database will be replaced in the next few years by the development of the product, substance, organization and referential management systems PMS, SMS, OMS and RMS. These new systems are planned to be designed to support the synchronisation of data and is planned to be used for EudraVigilance as well. The recoding will be performed using ISO IDMP codes that will be available for everyone to use.</p> <p>The current requirement for re-routing of ICSRs to NCAs is that the original ICSR (R2 or R3 format) is re-routed unchanged; to populate sections of an ICSR that were not sent to by the originator would be a significant change to the re-routing requirements defined in the EU Implementation Guide.</p> |
| 4.26 | <p>In the Post-ISO-IDMP era: will existing ICSRs be recoded according to IDMP-requirements and if yes, will all of them re-routed to the MS once more?</p>  | <p>If MAHs will be sending ICSRs coded using ISO IDMP terminology, those ICSRs will be re-routed to NCAs in the coded format; if the IDMP codes are missing, the NCA could opt in to receiving a copy of the ICSR recoded by EMA against a suitable IDMP code if available.</p> <p>The requirements will need to be further assessed closer to the implementation of the ISO IDMP standards.</p>   |

| Ref. | Question  | Answer  |
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| 4.27 | Cases submitted by NCAs to EudraVigilance will not be retransmitted back to the sending NCA – i.e. the sending NCA will not be informed about the EV-case number, which might be a problem in case of any questions. Since retransmission check bases on the "batch sender identifier", in case of any new information sent by a second stakeholder, the originally sending NCA will get this new information by rerouting of the follow-up and the NCA's originally used case number will be part of the report duplicate section/wwcid – Is this correct? | <p>ICSRs will not be re-routed to the sending NCA. The EMA does not change the case number of any cases, and any case downloaded by an MAH would have the NCA's case number in, which could be used in case of questions.</p> <p>If another organisation e.g. sends an updated version (follow-up) of the ICSR to EudraVigilance, the applicable NCA(s) will receive the re-routed version of the ICSR regardless of what is entered in the report duplicate and WW case ID sections.</p> |
| 4.28 | Should the MAH submit Regulatory Authority reports they have downloaded and processed, back to the EMA?   | No, MAHs should not send back ICSRs they have downloaded from EudraVigilance; unless they have received new information from the primary source that qualifies for submission of a follow-up report as described in GVP Module VI.  |

| Ref. | Question  | Answer   |
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| 4.29 | If an MAH markets only in a few EU countries, can you confirm that they are not expected to download cases from other EU countries with the same active substance? Or are they still required to download and database all ICSRs? | <p>In accordance with the EudraVigilance Access Policy, Level 2A access also provides the name of the medicinal product as reported by the primary source (if provided). On this basis the MAH can review the ICSRs and determine "ownership" related to the medicinal products, for which they hold a marketing authorisation.</p> <p>Article 24 of the Regulation (EC) 726/2004 states that the EudraVigilance database "shall also be accessible to MAHs to the extent necessary for them to comply with their pharmacovigilance obligations". Such access is provided based on the Level 2A downloads to facilitate the oversight of the overall safety profile of an active substance independent of the route of reporting by the primary source either via an NCA or an MAH in the EEA.</p> <p>ICSRs, for which the MAH cannot exclude ownership as stated in GVP Module VI, should be processed by the MAH as part of their pharmacovigilance system. Chapter VI.C.2.2 states "Exclusion based on the primary source country or country of origin of the adverse reaction is possible if the marketing authorisation holder can demonstrate that the suspected medicinal product has never been supplied or placed on the market in that territory or that the product is not a travel medicine (e.g. anti-malarial medicinal product)."</p> |
| 4.30 | For the last revision of GVP Module VI, a tracked change version was available - will a tracked change version of this update be made available?  | <p>The track changes version of GVP VI Rev 2 is already published <a href="#">here</a>.</p> <p>The document is accessible on EMA website via the following pathway: Home/Human regulatory/Post-authorisation/Pharmacovigilance/Good Pharmacovigilance Practices/Archive of development of GVP.</p>   |
| 4.31 | What are the criteria of reports included in EudraVigilance? Are consumer case reports also included in the database?   | <p>All Individual Case Safety Reports (ICSRs) reported by health care professionals and non-health care professionals (including patients and consumers) are submitted to EudraVigilance by national competent authorities and marketing authorisation holders in line with the requirements detailed in chapter VI.C.4 (Submission modalities of ICSRs in EU) of GVP Module VI.</p>   |

| Ref. | Question  | Answer   |
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| 4.32 | <p>The amendment report in R3 allows the MAH to inform the agency if the batch number for biological medicines was asked, but the primary source did not respond to the request for information. However, is the expectation the same for users with an R2 database? Should we submit a follow up report following each request for information where we have not received a response, or only after the appropriate number of attempts has been made? And should the LRD be the date of the original report, if no response is received (therefore potential late case)?</p> | <p>In line with the guidance provided in chapter VI.C.6.2.2.7. Of GVP Module VI, follow-up ICSRs should be submitted if significant new medical information has been received on the ICSR.</p> <p>As outlined in chapter VI.B.3. of GVP Module VI, the batch number for suspected biological medicinal products is one of the elements, where the outcome of the follow-up is considered significant and is important to be notified.</p> <p>It is recommended to specify in the case narrative if information on the batch number has been requested, when it is missing in the initially submitted ICSR for suspected biological medicinal products.</p> <p>In accordance with ICH-E2B(R2 or R3) guideline, an amendment report or follow-up report should be submitted to clarify if, after an appropriate number of attempts specified in the organisation procedures/work instruction, it was not possible to obtain follow-up information from the primary source on the batch number of the suspected biological medicinal product.</p> |

| Ref. | Question   | Answer  |
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| 4.33 | <p>Rev 2 of GVP Module VI states that MAHs shall not submit literature cases that are in scope of MLM. What if the literature case explicitly names our product? Are we still expected to wait and see if MLM will detect and evaluate the case? (If the article is MEDLINE-based, we may be aware of the case months earlier than the MLM service provider)</p> | <p>With regard to the screening of the medical literature, the requirements provided in GVP Module VI are part of the marketing authorisation holder obligations in relation to:</p> <ul style="list-style-type: none"> <li>i. The submission of individual cases of suspected adverse reactions;</li> <li>ii. The wider literature searches which need to be conducted for periodic safety update reports.</li> </ul> <p>Regarding ICSR submission to EudraVigilance from cases identified in the literature, reference is made to Chapter VI.C.2.2.3.1 'Monitoring of the medical literature by the European Medicines Agency' of GVP VI Revision 2 which specifies, that "In accordance with Article 107(3) of Directive 2001/83/EC and to avoid the submission of duplicate ICSRs, the marketing authorisation holder (MAH) shall only submit those ICSRs described in the medical literature which is not reviewed by the Agency, for all medicinal products containing active substances which are not included in the list monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004."</p> <p>As part of the wider literature searches which need to be conducted for periodic update reports, MAHs should monitor medical literatures for the active substances contained in their medicinal products. They shall however not submit resulting ICSRs if monitoring is also done by the Agency for those medical literatures and actives substances.</p> <p>In practice, if you find an article which the MLM service has not yet found, from a journal that the MLM service is monitoring, you can inform the MLM service and they will obtain the article and make a case within 7 days.</p> |

| Ref. | Question   | Answer  |
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| 4.34 | <p>When will implementation of the ISO IDMP come into effect for E2B(R3)?</p> <p>The "ICH guideline E2B(R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide" refers in section 3.2.1.1. to the ISO IDMP, specifically to ISO standards 11238, 11239, 11240, 11615, and 11616 (on p16). However, the guide says that until these vocabularies are available then temporary rules in each region should be used.</p> <p>The ISO standard referred to have been published in 2012 and are available on the ISO website. I.e. these standards were available prior to publication of the R3 implementation guide. So should these existing 2012 ISO standard be used when preparing E2B R3 files? If not then what is the trigger for these standards considered to "be available" from the EMA perspective? I did not find any reference to E2B(R3) in the SPOR document. Should we start using the existing ISO standards once we start using the R3 format?</p> | <p>The ISO IDMP suite of standards was initially published in 2012. In order for those standards to be implemented in a compatible and fully harmonised manner, ISO has been working on ISO IDMP Technical Specifications and on a revised version of the ISO IDMP suite of standards. Some of them are planned to be published towards the end of 2017 and the final set of documents should be made available during 2018.</p> <p>Once the Standards and the Technical Specification documents are published, it will be necessary to build an ISO IDMP compatible repository which is a prerequisite for the capability to code information on medicinal products and substances in ICSR E2B(R3) messages.</p> <p>The European Regulatory Network in participation with pharmaceutical industry is running a set of projects, known as S.P.O.R., to build ISO IDMP compatible vocabularies (see more details at <a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000645.jsp&amp;mid=WC0b01ac058078fbe2">http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000645.jsp&amp;mid=WC0b01ac058078fbe2</a>). Once the vocabularies will be made available, EMA will communicate how and when their use will become applicable within the EudraVigilance system for transmission of ICSR E2B(R3) messages.</p> |

| Ref. | Question  | Answer  |
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| 4.35 | In case of FUP requests should we contact NCAs or EMA? How is the process planned?  | <p>NCAs will submit follow-up information to EudraVigilance if new information is received.</p> <p>MAHs should not routinely contact NCAs. Please see GVP Module VI -VI.C.2.2. Responsibilities of the marketing authorisation holder in the EU:</p> <p>"For the ICSRs made accessible to a marketing authorisation holder from the EudraVigilance database in accordance with Article 24(2) of Regulation (EC) No 726/2004 and in line with the EudraVigilance Access Policy for Medicines for Human Use, the routine request for follow-up by the marketing authorisation holder is not foreseen. If the follow-up of an ICSR is necessary for a specific situation, a justification should be provided with the request, which should be addressed directly to the sender organisation of the ICSR".</p> |
| 4.36 | For an EU only MAH - is it acceptable they do not download each ICSR into their safety database, but append summary tabulations based on EVDAS outputs to their PSURs?                                  | <p>On 23 July 2018 EMA published guidance to clarify the obligations of marketing authorisation holders to record information on ICSRs they access in Eudravigilance.</p> <p><a href="#">Note for clarification: Recording by marketing authorisation holders of information on suspected adverse reactions held in EudraVigilance</a> for MAHs on the recording of ICSRs accessed in EudraVigilance. It provides clarification on the obligations of MAHs on how to record information on suspected adverse reactions accessed in EV.</p>  |
| 4.37 | EU ICSR Implementation Guide states that E.i.9 (R2 field: A.1.2) allows ISO values, including the value "EU". As EU is not an ISO code, will we expect to see ICSRs with a country of occurrence of EU? | <p>ISO 3166 standard does include the value "EU" as an exceptionally reserved code. The current EudraVigilance access policy for L2 grants access to the original data of this field.</p>   |
| 4.38 | Can you please share the list of countries part of the EEA for which the simplified reporting rules apply?  | <p>It applies to all EEA Member States.</p>   |

| Ref. | Question  | Answer   |
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| 4.39 | GVP Module VI (Revision 2), Chapter VI.C.6.2.2.4. 'Case narrative, comments and causality assessment' states "a case narrative shall be provided, where possible, for all cases with the exception of non-serious cases." Our internal process require us to enter narratives into our non-serious cases and therefore is it ok to submit our non-serious ICSRs to EV with a narrative? | You are not <i>required</i> to create a narrative for non-serious cases, but you may if you wish |

| Ref.                             | Question  | Answer                                       |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
|----------------------------------|---|--|------------------|----------|---------|-----------------------------|---------|----------|-----------|------------------|------------|-----------|--|-------|------------|----------------------------|---------|----------|---------------------------|----------------------------------|-------------|------------|---------------|--------|---------------------------|--------------------------------|------------|--|----------------|---------|------------------------|---------|--------|--------------------------|----------------------------|------------|--------------------|---------------|----------------------|-------------------------|---------------|---------------|-------------------|--|
| 4.40                             | <p>Please confirm whether or not the below territories rightfully "belong" under EEA legislation and subsequently if the reporting rules should follow EEA or ex-EEA legislation. If our understanding does not match with EMA expectations, our reporting compliance for non-serious reports could be impacted.</p> <table border="1"> <tr> <td>Aland Islands</td> <td>French Polynesia</td> <td>Pitcairn</td> </tr> <tr> <td>Andorra</td> <td>French Southern Territories</td> <td>Reunion</td> </tr> <tr> <td>Anguilla</td> <td>Gibraltar</td> <td>Saint Barthelemy</td> </tr> <tr> <td>Antarctica</td> <td>Greenland</td> <td>Saint Helena, Ascension and Tristan da Cunha</td> </tr> <tr> <td>Aruba</td> <td>Guadeloupe</td> <td>Saint Martin (French Part)</td> </tr> <tr> <td>Bermuda</td> <td>Guernsey</td> <td>Saint Pierre and Miquelon</td> </tr> <tr> <td>Bonaire, Sint Eustatius and Saba</td> <td>Isle of Man</td> <td>San Marino</td> </tr> <tr> <td>Bouvet Island</td> <td>Jersey</td> <td>Sint Maarten (Dutch Part)</td> </tr> <tr> <td>British Indian Ocean Territory</td> <td>Martinique</td> <td>South Georgia and the South Sandwich Islands</td> </tr> <tr> <td>Cayman Islands</td> <td>Mayotte</td> <td>Svalbard and Jan Mayen</td> </tr> <tr> <td>Curacao</td> <td>Monaco</td> <td>Turks and Caicos Islands</td> </tr> <tr> <td>Falkland Island (Malvinas)</td> <td>Montserrat</td> <td>Vatican City State</td> </tr> <tr> <td>Faroe Islands</td> <td>Netherlands Antilles</td> <td>Virgin Islands, British</td> </tr> <tr> <td>French Guiana</td> <td>New Caledonia</td> <td>Wallis and Futuna</td> </tr> </table> | Aland Islands                                | French Polynesia | Pitcairn | Andorra | French Southern Territories | Reunion | Anguilla | Gibraltar | Saint Barthelemy | Antarctica | Greenland | Saint Helena, Ascension and Tristan da Cunha | Aruba | Guadeloupe | Saint Martin (French Part) | Bermuda | Guernsey | Saint Pierre and Miquelon | Bonaire, Sint Eustatius and Saba | Isle of Man | San Marino | Bouvet Island | Jersey | Sint Maarten (Dutch Part) | British Indian Ocean Territory | Martinique | South Georgia and the South Sandwich Islands | Cayman Islands | Mayotte | Svalbard and Jan Mayen | Curacao | Monaco | Turks and Caicos Islands | Falkland Island (Malvinas) | Montserrat | Vatican City State | Faroe Islands | Netherlands Antilles | Virgin Islands, British | French Guiana | New Caledonia | Wallis and Futuna | <p>Article 11(1) of Commission Implementing Regulation (EU) No 520/2012 makes provision for the imposition of certain compliance management obligations which are pertinent to quality system procedures and processes, as regards pharmacovigilance of medicinal products. In particular, sub-paragraph c requires the following: "the submission of accurate and verifiable data on serious and non-serious adverse reactions to the EudraVigilance database within the time limits provided for in the first and second subparagraphs respectively of Article 107(3) of Directive 2001/83/EC."</p> <p>Based on the understanding that the application of Article 11(1)(c) is at the centre of the query, it then follows that the key question is whether it is intended to apply to the territories identified in the relevant list.</p> <p><u>Application of Article 11(1)(c) of the Commission Implementing Regulation to OCTs:</u></p> <p>As an initial observation, it is useful to refer to Article 198 TFEU (ex Article 182 TEC), which provides that: "The Member States agree to associate with the Union the non-European countries and territories which have special relations with Denmark, France, the Netherlands and the United Kingdom. These countries and territories (hereinafter called the 'countries and territories') are listed in Annex II". Council Decision 2013/755/EU on the association of the overseas countries and territories (OCTs) with the European Union is also instructive in determining the application of EU law to OCTs. In particular, Recital 4 to the said Council Decision provides that:</p> <p>"The TFEU and its secondary legislation do not automatically apply to the OCTs, with the exception of a number of provisions which explicitly provide for the contrary. Although not third countries, the OCTs do not form part of the single market and must comply with the obligations imposed on third countries in respect of trade, particularly rules of origin, health and plant health standards and safeguard measures".</p> <p>The aforementioned recital sets out the general principle according to which EU law does not apply to the OCTs unless the contrary is explicitly provided for.</p> <p>In light of the above, the general principle is that the EU acquis on medicinal products is not applicable to OCTs associated with the EU/EEA, unless there is express provision to the contrary.</p> <p>Further, EMA have not identified any provision contained within EU pharmacovigilance legislation, which would suggest that such measures are applicable to the OCTs.</p> |
| Aland Islands                    | French Polynesia  | Pitcairn                                     |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| Andorra                          | French Southern Territories   | Reunion                                      |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| Anguilla                         | Gibraltar   | Saint Barthelemy                             |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| Antarctica                       | Greenland   | Saint Helena, Ascension and Tristan da Cunha |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| Aruba                            | Guadeloupe  | Saint Martin (French Part)                   |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| Bermuda                          | Guernsey  | Saint Pierre and Miquelon                    |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| Bonaire, Sint Eustatius and Saba | Isle of Man   | San Marino                                   |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| Bouvet Island                    | Jersey  | Sint Maarten (Dutch Part)                    |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| British Indian Ocean Territory   | Martinique  | South Georgia and the South Sandwich Islands |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| Cayman Islands                   | Mayotte   | Svalbard and Jan Mayen                       |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| Curacao                          | Monaco  | Turks and Caicos Islands                     |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| Falkland Island (Malvinas)       | Montserrat  | Vatican City State                           |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| Faroe Islands                    | Netherlands Antilles  | Virgin Islands, British                      |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |
| French Guiana                    | New Caledonia   | Wallis and Futuna                            |                  |          |         |                             |         |          |           |                  |            |           |  |       |            |                            |         |          |                           |                                  |             |            |               |        |                           |                                |            |  |                |         |                        |         |        |                          |                            |            |                    |               |                      |                         |               |               |                   |  |

| Ref. | Question  | Answer   |
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| 4.41 | As per updated GVP VI.B.1.1.1: cases from multiple reporters in which at least one notification arose spontaneously should be treated as a spontaneous report. If a report from a clinical trial is originally received and sent to EVCTM but follow-up is then received spontaneously would EMA then expect the MAH to send to EVHUMAN or to EVCTM? Or both? | <p>If the investigator becomes aware of serious adverse events occurring to a subject after the treatment of that subject has ended, they should be reported to the sponsor in line with the guidance provided in Chapter 4.4 of the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'). These reports should be submitted to EVCTM by the sponsor based on the requirement provided in CT3 Guidance.</p> <p>If a follow-up report is received spontaneously outside of the organised data collection scheme of the clinical trial, it should be reported to EVPM. Detailed information regarding the clinical trial should be provided in the relevant section of the ICSR which should be submitted as spontaneous report.</p> |
| 4.42 | Concomitant therapies interacting with IMP or individually causing an AE, how do we capture the causality?  | The degree of suspected relatedness of each medicinal product to each reported adverse reaction can be presented in a structured manner in the ICSR. Information should be provided in the relevant ICH E2B data elements and section. See subsection C of Chapter VI.C.6.2.2.4. (Case narrative, comments and causality assessment).  |
| 4.43 | If an NCA has sent a non-serious case before 22nd November to MAH and WHO and the case is not in EV and we need to nullify the case (either because it is a duplicate or because it is now non-valid), will the case be rejected when we submit this? If yes, then how should we communicate this information to MAH and WHO?                                 | <p>As a general principle, it is not possible to nullify a case if no ICSR related to the case is stored in EudraVigilance.</p> <p>If this is required, you will need to liaise directly with the concerned MAH and WHO UMC to ask them to "nullify the case".</p>   |

| Ref. | Question  | Answer   |
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| 4.44 | Will non-serious cases with a receive/receipt date before 22nd November, but with a transmission date after 22nd November (or after 24th November/cutover legacy period) be included in compliance calculations?  | Yes, if you transmit it to EV, then it will be included in the compliance calculations   |
| 4.45 | Will EMA follow up with MAHs if follow up is requested on majority of cases or close to all cases?- Background info: In practice we experience that some MAHs request follow up on majority or close to all cases | <p>The follow-up process is defined in GVP Module VI.</p> <p>As a general principle the follow-up should always be performed by the sender organisation (the organisation that received the report from the primary source and sent it to EVPM).</p> <p>There are instances where an NCA may involve the MAH to perform the follow-up which is again explained in <a href="#">GVP Module VI revision 2</a> (please see appendix 1 process for follow-up of ICSRs).</p> |
| 4.46 | Is there an expectation from EMA that MAH should provide information on Amendments in Narrative; this is when an amendment is submitted in ICH-E2b R2 Format?   | Regardless of the format, MAHs should follow the guidance in GVP Module VI, Chapter VI.C.6.2.2.8. Amendment of cases: In line with ICH-E2B the following applies for the submission of amendment ICSRs.  |

| Ref. | Question   | Answer   |
|------|--|--|
| 4.47 | When primary source qualification is not available, should we have to select "unknown", as per to E2B(R3) or consumer, as per to GVP Module VI?  | <p>You should select consumer. As stated in GVP Module VI, Chapter VI.B.2 "Validation of reports", Section a. "one or more identifiable reporter"</p> <p>"In line with ICH-E2D, the term 'identifiable' indicates that the organisation notified about the case has sufficient evidence of the existence of the person who reports the facts based on the available information. In addition, in accordance with ICH E2B, an ICSR is not valid for submission unless information concerning the qualification and the country is available for at least one reporter. Thus, an ICSR is valid if the rules from ICH-E2D regarding the reporter's identifiability and from ICH-E2B regarding the reporter's qualification and country are fulfilled for at least one reporter. <u>If information on the reporter's qualification is missing, the notification should be considered by default as a consumer report.</u> If information on the reporter's country is not available, the country where the notification was received or where the review took place should be used in the ICSR."</p> |
| 4.48 | We used to receive the cases by brand name from Health Authorities (i.e. Spanish Health Authorities). From 22-Nov-2017, we frequently receive cases where the brand name is not mentioned. Should we assume that we are the owner of these products? | <p>Yes, if there is no brand name mentioned in a case and you market the product in that territory, then you cannot exclude ownership on that basis and should assume that the case may be related to your product.</p>  |
| 4.49 | Please can you confirm if the French imputability will remain a requirement as of 22 November 2017 when the simplified reporting rules will become applicable?   | <p>For ICSRs occurring in France, the drug causality assessment according to the French imputability method is no longer obligatory for pharmaceutical companies. The drug causality assessment remains however mandatory.</p> <p>Please refer to the <a href="#">public guidance published by ANSM</a></p>  |

| Ref. | Question  | Answer  |
|------|---|---|
| 4.50 | When submitting literature articles, does this have to be in the ICH E2B(R3) format?  | <p>Please follow <a href="#">GVP module VI</a>, chapter VI.App.2.10. "Electronic submission of copies of articles on suspected adverse reactions published in the medical literature".</p> <p>There is no requirement to provide routinely copies of articles published in the medical literature. In accordance with Article 28(3) of the Commission Implementing Regulation (EU) No 520/2012, upon request of the Agency, the marketing authorisation holder that transmitted the initial report shall provide a copy of the relevant article taking into account copyright restrictions, and a full translation of that article into English.</p> <p>If you are transmitting in E2B(R3) format, then the requested article &amp; translation, where applicable, should be attached to the case. If you are still transmitting in E2B(R2) format, then the requested article should be emailed to <a href="mailto:evlit@ema.europa.eu">evlit@ema.europa.eu</a> as before.</p> |
| 4.51 | Are individual country requirements still expected for cases being submitted to the EMA? For example French Imputability, Spanish case narrative? | <p>The Good pharmacovigilance practices (GVP) are a set of measures drawn up to facilitate the performance of pharmacovigilance in the European Union (EU). GVP apply to marketing-authorisation holders, the European Medicines Agency and medicines regulatory authorities in EU Member States.</p> <p>They cover medicines authorised centrally via the Agency as well as medicines authorised at national level. GVP Module VI defines the requirements for the collection, management and submission of reports of suspected adverse reactions to medicinal products in the EU.</p> <p>For country specific requirements such as the use of local language requirements please liaise with the national Competent Authorities in the EEA. For French imputability, see question 4.58</p>   |

| Ref. | Question  | Answer  |
|------|---|---|
| 4.52 | <p>If the reported adverse event is related to concomitant therapy and not to the suspect medicinal product, per section I.C.3.5 of EU ICSR Implementation Guide (EMA/51938/2013), the case qualifies as SUSAR for expedited reporting. In this instance, how do we capture causality to the concomitant therapy?</p> | <p>Reference is made to chapter VI.C.1.1. 'Management of individual safety reports for clinical trials' of GVP Module VI revision2:</p> <p>Where an untoward and unintended response from a clinical trial conducted in accordance with Directive 2001/20/EC is suspected to be related only to a medicinal product other than the IMP and does not result from a possible interaction with the IMP, it should be managed in line with the requirements provided in Art 107(3) and 107a (4) of Directive 2001/83/EC. The same applies when the adverse reaction is suspected to be related only to an authorised non-investigational medicinal product (NIMP). In this context, the investigator or the sponsor is encouraged to report the case to the competent authority in the Member State where the reaction occurred or to the marketing authorisation holder of the suspected medicinal product, but not to both to avoid duplicate ICSRs submission. Where made aware of such case, the competent authority or the marketing authorisation holder should apply the time frames and modalities described in Chapter VI.C.3., VI.C.4. and VI.C.6. of GVP Module VI. The report should be managed, classified and submitted as spontaneous and the guidance detailed in Chapter VI.C.6.2.3.7. Subsection 3 of GVP Module VI should be followed with regard to the electronic submission of ICSRs.</p> <p>The degree of suspected relatedness of each medicinal product to each reported adverse reaction can be presented in a structured manner in the ICSR. It can be expressed for multiple sources (reporters, competent authorities, marketing authorisation holders) while using multiple methods of causality assessment. The guidance provided in Chapter VI.C.6.2.2.4. 'Case narrative, comments and causality assessment' of GVP Module VI should be followed for the provision of this information in ICSRs line with ICH-E2B.</p> |

| Ref. | Question   | Answer  |
|------|--|---|
| 4.53 | <p>An MAH/NCA receives a non-serious case. Subsequently, before the case has been transmitted to EV, follow-up is received that makes the case serious.</p> <p>Should the initial and follow-up information be combined when the case is submitted?</p> <p>Which dates should be entered into the fields "Date Report Was First Received from Source" (R3 C.1.4/R2 A.1.6b) &amp; "Date of Most Recent Information for this Report" (R3 C.1.5/R2 A.1.7b)?</p> <p>Which clock would be counted? 15 or 90 days?</p> | <p>The principle to consider is that the receipt of new information does not reset/extend the clock start date of the legal obligation for submission of the information. The clock starts when you have the minimum criteria for a valid ICSR as outlined in GVP Module VI.</p> <p>Organisations can combine the information into one report however the Date of Most Recent Information for this Report" (R3 C.1.5/R2 A.1.7b) should reflect the earliest date the case became reportable.</p> <p>In this situation, if you were to combine the initial and follow-up into one report, then the 15-day clock would apply. Therefore, the most pragmatic solution would be to complete the non-serious initial report as soon as possible and transmit it, and then send the serious follow-up within 15 days of receipt of the information which made the case serious.</p> |

| Ref.                     | Question  | Answer   |
|--------------------------|---|--|
| 4.54                     | <p>What are the MAH's obligations regarding downloading of ICSR from EudraVigilance that were transmitted by MAHs:</p> <p>Are MAHs supposed to process ICSRs submitted by other MAHs to EudraVigilance if the information does not allow excluding that the suspected product might be a product of the MAH even if this might lead to duplication of ICSRs?</p> <p>What is the expectation if a downloaded ICSR contains the MAH product name as a subsequent suspected product?</p> | <p>On 23 July 2018 EMA published guidance to clarify the obligations of marketing authorisation holders to record information on ICSRs they access in Eudravigilance.</p> <p><a href="#">Note for clarification: Recording by marketing authorisation holders of information on suspected adverse reactions held in EudraVigilance</a> for MAHs on the recording of ICSRs accessed in EudraVigilance. It provides clarification on the obligations of MAHs on how to record information on suspected adverse reactions accessed in EV.</p>   |
| 4.55<br><b>(updated)</b> | <p>How should MAHs process ICSRs made accessible via AIFA's national pharmacovigilance database?</p>  | <p>AIFA is recording information on suspected adverse reactions related to medicines and reported by patients and healthcare professionals in its national pharmacovigilance database. Valid cases of suspected adverse reactions are then submitted to EudraVigilance.</p> <p>On 15<sup>th</sup> May 2018 AIFA's national pharmacovigilance database was modified in order to register, only as free text format (in the case narrative), the data elements that not map to the ICH E2B (R2) ICSR format (e.g. medication errors, place of vaccination, use of other substances different from drug e.g. food supplements).</p> <p>Therefore, from 15 May 2018, MAHs are no longer required to seek these elements in the national pharmacovigilance database because this additional information are included in the case narrative so to be available in EudraVigilance. Furthermore the italian cases are no more accessible to MAHs via AIFA's national pharmacovigilance database.</p> |

| Ref.                 | Question   | Answer   |
|----------------------|--|--|
| 4.56<br><b>(new)</b> | If we have been informed by an NCA about a case and we have additional data from the primary source, but the case is not yet uploaded by the NCA, what should we do? Should we report the case to EV or communicate first with the NCA to see how to handle this issue? In order not to have duplicates? | NCA's should not normally inform you directly about a case before it has been submitted to EudraVigilance. If you receive information directly from the primary source that is enough to create a valid case you will have 15-days to submit it to EudraVigilance. If the NCA submits the case to EV before you do and you become aware of this submission you can add in the additional information and NCA case identifiers into your own submission. If you are aware that both you and an NCA have both submitted the same case due to both having contact with the primary source you can report these duplicates through the EMA Service desk <a href="#">Report Duplicates for ICSR</a> . |
| 4.57<br><b>(new)</b> | Can an MAH use the source as Regulatory in case we are sending a FU in a Regulatory Case (already submitted initially to EV by the NCA)?   | No, MAHs should not submit their own version(s) of cases submitted to EV by NCA's (or other MAHs). If you receive information directly from primary source they are the source of the information not the regulatory authority. The Primary source is the person that has direct contact with the patient or is the patient themselves; the primary source is never the recipient or secondary recipient of an ICSR.   |

## 5. Reporting to National Competent Authorities in the EEA

| Ref. | Question   | Answer  |
|------|--|---|
| 5.1  | Will MAHs receive EU ICSRs reported by NCAs ONLY from the EMA? | <p>For the detailed legal provisions on the simplified reporting rules please refer to the <a href="#">announcement of the EMA Management Board on the confirmation of full functionality of the EudraVigilance database</a> and GVP Module VI Chapter VI.C.2.1 (Responsibilities of Member States) which states the following:</p> <p>"Each Member State shall have in place a system for the collection and recording of unsolicited and solicited reports of suspected adverse reactions that occur in its territory and which are brought to its attention by healthcare professionals, consumers, or marketing authorisation holders [DIR Art 101(1) and 107a(1)].</p> <p>In this context, competent authorities in Member States shall establish procedures for collecting and recording all reports of suspected adverse reactions that occur in their territory [IR Art 15 (2)]. Marketing authorisation holders shall submit ICSRs to EudraVigilance in accordance with the provisions set out in Dir Art 107(3) and further detailed in VI.C.4."</p> <p>In addition, Article 107a, paragraph 4 states the following:</p> <p>"Member States shall, within 15 days following the receipt of the reports of serious suspected adverse reactions referred to in paragraph 1, submit the reports electronically to the EudraVigilance database. They shall, within 90 days from the receipt of reports referred to in paragraph 1, submit reports of non-serious suspected adverse reactions electronically to the EudraVigilance database. Marketing authorisation holders shall access those reports through the EudraVigilance database".</p> |
| 5.2  | Do Spanish non-serious cases require a Spanish narrative?      | <p>Where suspected adverse reactions are reported by the primary source in narrative and textual descriptions in an official language of the Union other than English, the original verbatim text and the summary thereof in English shall be provided by the marketing authorisation holder [IR 28(4)].</p> <p>In practice, for ICSRs reported in Spain, the original verbatim text reported by the primary source in Spanish should be included in the ICSRs. This is applicable to serious and non-serious cases. For non-serious cases there is no need to create a case narrative if not provided by the primary source.</p>   |

| Ref. | Question  | Answer   |
|------|---|--|
| 5.3  | <p>Does EMA plan to include additional national requirements and specialties within the E2B file for submission to EMA into official EMA guidelines, e.g. ICSRs occurring in Spain to contain a Spanish narrative?</p> <p>As we do not have reporting obligations to local authorities any longer we expect the EMA requirements to be the driving set of rules for a compliant E2B file.</p> | <p>In accordance with Article 28 (3)(m) of the Commission Implementing Regulation (EU) No 520/2012, a case narrative shall be provided, where possible , for all cases with the exception of non-serious cases.</p> <p>With regard the provision of information in the local language the following requirement from Article 28 (4) of the Commission Implementing Regulation (EU) No 520/2012 applies: Where suspected adverse reactions are reported by the primary source in narrative and textual descriptions in an official language of the Union other than English, the original verbatim text and the summary thereof in English shall be provided by the marketing authorisation holder.</p> <p>In practice, the original verbatim text reported by the primary source in an official language of the Union other than English should be included in the ICSR, if it is requested by the Member State where the reaction occurred or by the Agency. The ICSR should be completed and submitted in English if not otherwise requested.</p> <p>The case narrative in the local language and the summary thereof in English should be provided in serious ICSRs submitted to EudraVigilance if requested by the competent authority of the Member State where the reaction occurred. If not otherwise requested, the narrative should be provided in English.</p> |

| Ref. | Question  | Answer   |
|------|---|--|
| 5.4  | Does the EMA expect that ICSRs provided by NCA to EMA be made available in English language in all E2B free text fields?  | <p>With regard the provision of information in the local language the following requirement from Article 28 (4) of the Commission Implementing Regulation (EU) No 520/2012 applies: Where suspected adverse reactions are reported by the primary source in narrative and textual descriptions in an official language of the Union other than English, the original verbatim text and the summary thereof in English shall be provided by the marketing authorisation holder.</p> <p>In practice, the original verbatim text reported by the primary source in an official language of the Union other than English should be included in the ICSR, if it is requested by the Member State where the reaction occurred or by the Agency. The ICSR should be completed and submitted in English if not otherwise requested.</p> <p>In accordance with Article 28 (4) of the Commission Implementing Regulation (EU) No 520/2012, Member States may report case narratives in their official language(s).</p> <p>For those reports, case translations shall be provided by the Member State when requested by the Agency or other Member States for the evaluation of potential signals. For suspected adverse reactions originating outside the EU, English shall be used in the ICSR.</p> |
| 5.5  | What are the EMA expectations for translation of ICSRs received at NCA, e.g. could the MAH be involved into translation of ICSRs originally reported to an NCA? | <p>In accordance with Article 28 (4) of the Commission Implementing Regulation (EU) No 520/2012, Member States may report case narratives in their official language(s). For those reports, case translations shall be provided by the Member State when requested by the Agency or other Member States for the evaluation of potential signals. For suspected adverse reactions originating outside the EU, English shall be used in the ICSR [IR 28 (4)].</p>  |

## 6. Guideline on good pharmacovigilance practices: Module IX - Signal Management

Please note that GVP Module IX questions are addressed in the [signal management Q&A document](#).

## 7. Signal detection and use of the MAH pharmacovigilance queries dashboard in EVDAS

Please note that for future versions of this Q&A document, signal detection and management questions will be addressed in the [signal management Q&A document](#) and EVDAS questions will be covered in the [EVDAS user manual](#), which will include a troubleshooting section.

## 8. Technical Questions

| Ref. | Question   | Answer  |
|------|--|---|
| 8.1  | In the ICSR Implementation Guide it is mentioned that "When binary (base 64) data is submitted the deflate algorithm RFC 1951 should be used "DF". Will EMA support any other compression logic like GZ?                 | The EU implementation of "DF" matches the ICH E2B(R3) Implementation Guide (IG).<br>If the ICH IG is updated then GZ will be implemented in EU as well. |
| 8.2  | When can we expect sample files having attachments?  | Example files have been created and published on the <a href="#">EMA website</a> .  |
| 8.3  | What will be the sequence of attachment embedding in the ICH E2B(R3) file?<br><br>Our interpretation is that it will be created using following sequence: Original Attachment > Compression with DF > Encoded to Base64. | Yes that is the normal approach as only base 64 notations can appear in the XML field.  |

| Ref. | Question  | Answer   |
|------|---|--|
| 8.4  | <p>In the latest EMA BFC package, there is change in the file downgrade-b4.xsl starting from line 289. We are not able to find any documentation, in which this change is covered or explained:</p> <pre data-bbox="315 501 741 1099"> &lt;xsl:if test="\$XEVMPPD=1"&gt;&lt;xsl:choose&gt;  &lt;xsl:when test="string- length(hl7:code/@displayName) &gt; 0 and string-length(hl7:code/@code) &gt; 0 and hl7:code/@codeSystem ='SUB-code'"&gt;&lt;xsl:value-of select="hl7:code/@displayName"/&gt;&lt; /xsl:when&gt;  &lt;xsl:otherwise&gt; &lt;xsl:value-of select="hl7:name"/&gt;&lt;/xsl:otherwise &gt;&lt;/xsl:choose&gt;&lt;/xsl:if&gt; &lt;xsl:if test="\$XEVMPPD!=1"&gt; &lt;xsl:value-of select="hl7:name"/&gt;&lt;/xsl:if&gt; &lt;/xsl:if&gt; </pre> | <p>An organisation can choose between using the verbatim reported product and substance names and the classified XEVMPD terms made by EMA for population of the ICH E2B(R2) data element.</p> <p>The setting can be applied in the BFC file "OIDs.xsl":</p> <pre data-bbox="748 405 2060 469"> &lt;!-- Use Recoded EudraVigilance product and substance names instead of verbatim term --&gt;&lt;!-- set value to 1 to use EV recoding--&gt;&lt;xsl:variable name="XEVMPPD"&gt;&lt;/xsl:variable&gt;&lt;!-- EV product --&gt; </pre> |

| Ref. | Question   | Answer   |
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| 8.5  | <p>Will the recoding for suspect drug substance or product names performed by EMA in the EudraVigilance database assign the corresponding MAH in B.4.k.4.3 / G.k.3.3. if this information is available?</p> <p>Does the EMA filter allow to define downloads based on product level, thus, allows for searches for fixed dose combinations to only list ICSR which actually contain the combination product?</p> | <p>The product and substance information reported in an ICSR is classified against data held in XEVMPD. The access policy is based on active substance; therefore MAHs will need to decide what action to take on the ICSRs downloaded based on the information as reported in the ICSR.</p> |
| 8.6  | <p>Can MAHs test L2B access in XCOMP?</p>  | <p>It is possible to test L2B requests in XCOMP, please make sure that the EU QPPV responsible has granted you L2B access through the "manage profile" option of the restricted area of EudraVigilance. L2B access is granted per individual user.</p>                                       |
| 8.7  | <p>Is there a R3 field viewer? So that we can see R3 files in human readable format to manually process?</p>   | <p>Yes, EVWEB allows organisations to upload E2B(R3) files into the application (workspace). From the application it is possible to generate human readable outputs.</p>   |
| 8.8  | <p>Have gateway validation rules to determine ACK and NACK from cases being transmitted been finalised for EMA? -.that is for R3 format ICSRs</p>  | <p>EU implementation guide and published business rules excel sheets include the rules applied for ICSRs and what issues would generate a negative acknowledgement being returned.</p>   |

| Ref. | Question  | Answer   |
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| 8.9  | Do R3 test files on EMA web site contain any attachments? What is the coding/archive standard for embedded files since there were some issues over its version? | As described in the EU implementation guide the encoding is Base64 and the compression algorithm is Deflate RFC1951 for sending in the EU, the test files have been amended and republished. |
| 8.10 | What is the maximum allowed embedded file size?   | As described in the EU implementation guide the maximum size of any single attachment is 15Mb, the maximum ICSR XML file size permitted is 20Mb.   |

| Ref. | Question  | Answer  |
|------|---|---|
| 8.11 | <p>Considering the effect of the EMA reclassifying ICSR data against the XEVMPD on receipt and implications for what the end-user would see as a result in any future download of this same re-coded ICSR data?</p> <p>Will the data in the product name remain as originally received from source? Or will the end user see a corrected version post re-coding against XEVMPD?</p> <p>If the latter statement is correct against what XEVMPD entry would we see the product name in the R3 message? (This is important to understand if there are multiple manufacturers of the same product)</p> <p>What happens if there is no supporting information to truly identify the correct MAH data (no formulation or route of administration)? What is the default?</p> | <p>The EU implementation guide has been updated and includes further details on how drugs are classified against XEVMPD data.</p> <p>In accordance with the access policy L2 access will provide the verbatim text as received in EudraVigilance for the product and substance names.</p> <p>In addition, the as-classified product/substance name will also be made available in a separate field.</p> <p>L2 access is given based on active substance(s).</p> <p>If you cannot exclude that a suspect/interacting drug is yours on the basis of one the following criteria: medicinal product name, active substance name, pharmaceutical form, batch number or route of administration, primary source country or country of origin (if you can demonstrate that the suspected medicinal product has never been supplied or placed on the market in that territory or that the product is not a travel medicine) in accordance with GVP Module VI Chapter VI.6.C.2.2, then the default assumption should be that it is yours</p> |

| Ref. | Question   | Answer  |
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| 8.12 | If the product name that is being provided is the original verbatim what exactly does the re-coding do – is it only Active substance information that is being re-coded?   | <p>The EU implementation guide has been updated and includes further details on how drugs are classified against XEVMPD data.</p> <p>Until ISO IDMP is implemented and can be used for ICSRs organisations will need to continue classifying reported verbatim product and substance names against their own product and substance dictionaries.</p>  |
| 8.13 | Will the filename for any download incorporate the date of download as part of the filename? this will help with managing reports where we may have potentially high volumes of reports upon download  | The data of creation of the XML file will be included within the XML files themselves using the field N.1.5   |
| 8.14 | As per 3_BFC Element Mapping v2_02, Field (R2) whose length is lesser than Field (R3) should be truncated and appended to narrative field. For example, say we have Field (in R3) whose length is 200 and the corresponding Field (in R2) length is 100, isn't only remaining 100 characters should be appended to narrative clinical tag? But we see entire 200 characters of Field (R3) is appended data in narrative. | <p>The ICH BFC document refers to the whole string being copied to the case narrative and the truncation is applied to the specific field:</p> <p><i>Truncate when downgrading to R2, indicate that the field has been truncated (e.g. with asterisk or ellipsis) and copy information to narrative section with identification of the information (e.g. sort of heading per element)</i></p> |

| Ref. | Question  | Answer   |
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| 8.15 | Is it necessary to have upgraded to the Latest version of Axway Gateway at EMA 5.12 to go through the testing?  | No, it is just a recommendation that you upgrade to the latest version in order to have the latest security updates and ensure that you can get full support from Axway. |
| 8.16 | We were not able to extract attachments from the test file '6. Literature with attachments' (DE-EMA-R3Testcase06) provided by EMA, as the block length did not match with its complement. We did not have this problem when we had extracted attachments from sample files provided by ICH: could you confirm that the documents were compressed in this test file using the deflate compression algorithm RFC 19514? | The test file has been updated with the release of the new version of XCOMP. The new test files use the compression algorithm RFC1951.                                   |
| 8.17 | The time-out "session expired" interval is very short for XCOMP – will this be the case for PROD as well?   | The session timeout is set to around ~20 minutes of no activity in the production system.  |

| Ref. | Question  | Answer   |
|------|---|--|
| 8.18 | <p>When EMA receives an ICSR and if a suspected medical product is either not coded to a specific tradename or coded to a non-existing tradename, will EMA then recode? Will EMA recode suspected medical products if the coding is not sufficient? Can you provide examples of such recoding? E.g. if Tradename is entered with spelling errors or if the tradename that is entered is actually the active ingredient.</p> | <p>Product and substance terms reported in ICSRs are recoded by EMA via a recoding algorithm.</p> <p>The recoding algorithm looks for an exact match between the product name reported in the ICSR and the product names submitted in the XEVMPD database; if a match is not found (e.g. reported product name is misspelled), the EMA will manually recode the incorrect reported name to the correct product name from the XEVMPD. For instance:</p> <p>ICSR reported medicinal product: PRODEME<br/>Medicinal product name in XEVMPD: PRODEMA</p> <p>In this case, because no exact match is found, the EMA will manually link the reported term PRODEME to PRODEMA, so that if PRODEME is reported again in new ICSRs, these ICSRs will automatically be associated to PRODEMA.</p> <p>The recoding algorithm looks for a match among the product names submitted in the XEVMPD, but also among the substance names; if an active ingredient is reported in the tradename section, the algorithm will look first for a match with product names, and as no results will be retrieved, it will continue looking for a match with substance names. For instance:</p> <p>ICSR reported medicinal product: CODEINE<br/>Medicinal product name in XEVMPD: -<br/>Substance name in XEVMPD: CODEINE</p> <p>In this case, the algorithm will first look for "CODEINE" among the product names (no results) and then move to the substance names, where a match can be found.</p> |

| Ref. | Question   | Answer   |
|------|--|--|
| 8.19 | <p>In instance reference file '00_EU_ICSR_Reference_Instance_v3_6', the codes for elements D.1.1.1 to D.1.1.4 (Patient medical record number(s) and source(s) of the record number) have specific numeric values (i.e. code="1" for D.1.1.1), meanwhile in EMA/CHMP/ICH/287/1995 (ICH guideline E2B(R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide), it is indicated that specific characters values must be used (i.e. code="gpmrn" for D.1.1.1). Could you clarify which codes must be used for these elements?</p> | <p>The published ICH and EU reference message instances should be used for the construction of valid XML files rather than the XML example snippets included in the ICH E2B (R3) implementation guide. The reference instances include the codes that are specified in the published ICH bilingual code lists. The ICH E2B (R3) download package includes all the bilingual code lists and reference instance that you should use.</p> |

| Ref. | Question  | Answer  |
|------|---|---|
| 8.20 | <p>In instance reference file '00_EU_ICSR_Reference_Instance_v3_6', the code systems for several elements as G.k.2.1.1b, G.k.2.1.2b, G.k.2.3.r.2b,etc are prefixed with 'TBD-' (i.e.: &lt;code code="G.k.2.1.2b" codeSystem="TBD-PhPID" codeSystemVersion="G.k.2.1.2a"/&gt;).Could you confirm that TBD stands for 'To be defined', and the correct codeSystem are the ones in the instance reference file without 'TBD-' implemented ?</p> | <p>Yes, TBD does stand for "To be defined", as the ISO IDMP standard is not yet available it is not yet possible to provide the codeSystem OIDs at this stage</p> |

| Ref. | Question   | Answer   |
|------|--|--|
| 8.21 | <p>When converting a E2B (R3) file using BFC, the seriousness criteria are systematically set to '1' in E2B (R2) when the value was originally set to 'true'. But according to ICH ICSR BFC Specifications, conversion logic for seriousness criteria must consider value of element E.i.3.1 (Term highlighted by reporter) associated: Could you clarify if a seriousness criteria should be set to '1' in R2 after conversion when the criteria was set to 'true' in R3, or only if the element E.i.3.1 has the value '3' (Yes, highlighted by the reporter, SERIOUS) or '4' (No, not highlighted by the reporter, SERIOUS) for this criteria?</p> | <p>As per the ICH BFC rules excel sheet, term highlighted is not used in the assignment of case seriousness.</p> |

| Ref. | Question  | Answer   |
|------|---|--|
| 8.22 | In an E2B(R3) file, when the element C.1.6.1 (Are Additional Documents Available?) has the value 'false', the corresponding R2 element A.1.8 has the value '1' after conversion by BFC. Actually, BFC systematically set the element A.1.8.1 with the value '1' regardless the value of C.1.6.1 in E2B(R3): could you clarify if there is an issue with BFC or if this is the expected behaviour? | For all E2B(R3) files converted to E2B(R2) there is an additional document, the original file was a different format and may contain additional structured data not available in the E2B(R2) file            |
| 8.23 | With regards to data privacy rules, should transmissions to EV include Patient Initials or not? If not, what about demographics data such as Age, DOB & Gender?   | Patient demographics should be provided if (a) they were provided to you and (b) you are not explicitly forbidden from sending them by data protection legislation in the country where the patient resides. |
| 8.24 | Which field is the compliance calculated against; "Date Report Was First Received from Source" (R3 C.1.4/R2 A.1.6b) or "Date of Most Recent Information for this Report" (R3 C.1.5/R2 A.1.7b) or is there an algorithm?   | Compliance is calculated between the official receipt date (Gateway date) and receipt of the latest information about the case (R3 C.1.5/R2 A.1.7b).   |

| Ref.                 | Question   | Answer  |
|----------------------|--|---|
| 8.25<br><b>(new)</b> | For companies submitting in E2B R2 and the only patient identifier we have is foetus because this does not export as R2 the case looks invalid in Eudravigilance because of no patient identifiers. We had several of these in our quality review spreadsheets (and replied back as such to EMA) but do you have any guidance on how we can export the information so these don't appear as invalid reports? | You should enter the word "Foetus" in the patient initials field. |

## 9. Testing procedures for Electronic Data Interchange (EDI) Partners

| Ref. | Question   | Answer   |
|------|--|--|
| 9.1  | What is the process to perform testing with EMA?   | <p>Following the launch of XCOMP on 26 June 2017, organisations can initiate testing. Only where major system changes are introduced by an organisation or the testing of E2B(R3) compliant systems is planned, EMA should be contacted to agree on a testing slot.</p> <p>Please refer to testing steps at the <a href="#">EudraVigilance: electronic reporting</a> webpage and the <a href="#">EudraVigilance change management</a> webpage.</p> |
| 9.2  | Is there any plan for EMA to provide any additional sample R3 files for organisations to validate the ICH E2B(R3) downgrade logic?   | Example files have been created and published on the EMA webpage. Organisations are able to produce their own ICH E2B(R3) test files through access to the new XCOMP EVWEB application.  |
| 9.3  | What constitutes an E2B(R3) compliant system? Does it have to have an E2B(R3) compliant safety database or is the capability to report in the E2B(R3) format sufficient to be an E2B(R3) compliant system? | The system should be able to create, send and process ICSRs that support all the data elements and the file format as defined in the ICH E2B(R3) and the EU ICSR Implementation guides. Testing should be performed as outlined in the EU ICSR Implementation Guide.   |
| 9.4  | <p>If we are EV Post users, is it mandatory to do the test in XCOMP?</p> <p>If it is necessary, should we book a slot?</p>   | <p>Yes, EVPOST users must test before being allowed to use EVPOST in production.</p> <p>To perform testing a testing slot needs to be booked with the dedicated area of service desk.</p> <p>In addition, please refer to the <a href="#">EudraVigilance Support Guide</a> for instructions on using the <a href="#">EMA IT Service Desk</a>.</p>  |

| Ref. | Question   | Answer  |
|------|--|---|
| 9.5  | When will cases be available in ICSR download functionality in the test environment, so we can download and test BFC tool and upload to our safety database to ensure functionality?   | Test ICSRs can already be downloaded from XCOMP, test files can be downloaded from the EudraVigilance pages on the EMA website.   |
| 9.6  | If an organisation has already submitted ICSRs to EV and is planning to continue to submit ICSRs in E2B(R2) format from November 2017, should testing with EMA be performed?   | It is recommended that all organisations test submission to the XCOMP system.<br><br>However, if you have not changed you R2 system there is no need to contact EMA for this testing; this can be performed in XCOMP yourselves.  |
| 9.7  | Does the EMA backward/forward conversion tool require another tool to actually convert R3 to R2, correct?<br><br>It at the very least requires an xslt converter and this tool is not qualified /approved by EMA, and therefore a company will need to validate it. We cannot use EMA conversion tool without any other tool, correct?<br><br>Is there a plan to make a 'qualified by EMA' tool to convert R3 to R2? | It is correct that you need to use a XSLT processor such as Microsoft's MSXSL in order to perform the instructions in the XSLT BFC tool.<br><br>It would be unusual for organisations to validate XSLT processors as organisations would not validate programing compliers such as for using Java programs. |

| Ref. | Question  | Answer   |
|------|---|--|
| 9.8  | If we are using EVWEB for transmission is testing (steps 1-6) required? Or just testing in XCOMP without booking a timeslot is enough?  | If you are only using EVWEB for creating and sending ICSRs there is no need to perform testing. Only gateway organisations and EVPOST users need to perform the testing.<br><br>It is recommended that EVWEB users follow the published eLearning courses and get familiar with XCOMP. |
| 9.9  | Would it be possible to download sample R3 files without accessing XCOMP? Can you share the files?  | Sample R3 files are published on the EMA website, under the page 'Electronic Reporting', section 'Step 5b: XML test phase for organisations using the E2B(R3) format'.<br><br>Please refer to the document 'EU reference instances' and 'EU E2B(R3) testing files'.                    |
| 9.10 | If the safety database vendor performs E2B R3 related testing with EMA directly, does the MAH using the tested safety database version still have to perform full testing or is this limited to few test scenarios? | In this scenario, if you have installed the database without modification, then you would not have to perform full testing.<br><br>If any modification has been done, testing with EMA is mandatory.   |
| 9.11 | Once the implementation of the new R3 format of the safety database is done, MAH has to performance the testing with EMA.<br><br>Are the places of the testing limited? First come and first served?                | Currently up to 5 organisations can book a place to perform test in a week.<br><br>This will be reviewed if testing requests increase.   |

## 10. Go-Live Planning

All questions relating to go-live planning have been removed from this Q&A document from version 1.4 (published March 2018) onwards.

## 11. Others

| Ref. | Question   | Answer  |
|------|--|---|
| 11.1 | When will you publish the update Q&A integrating the Q&A of the webinars?  | The Q&A document is intended to be updated monthly with the different questions received from all stakeholders, in particular with questions raised during support webinars organised by EMA.   |
| 11.2 | Will knowledge evaluation for e-learning be available for new users to get access to ICSR reporting in EudraVigilance or it is mandatory to undertake face-to-face training? | <p>The knowledge evaluation is intended for new non-commercial sponsors registering their organisation for the first time.</p> <p>There is no requirement for existing registered organisations using EVWEB to undertake the face-to-face training.</p> <p>Existing users of the system should follow the e-learning courses and do not need to take a competency assessment.</p> <p>New MAHs registering for the first time and wish to use EVWEB for their submissions will need to ensure that one member of staff has attended the training course.</p> |

| Ref. | Question  | Answer  |
|------|---|---|
| 11.3 | Can EMA provide an update on where IDMP stands and the plan/timeframe for use/implementation? | <p>The legacy EV data have been migrated from the current ICH E2B(R2) format in compliance with the Art.57/xEVMPD database.</p> <p>Art.57/xEVMPD database contains the core data elements as defined in the ISO IDMP standard.</p> <p>It serves as a comprehensive reference for information on medicinal product in the EEA and facilitates coding of medicines reported in reports originating from outside the EEA.</p> <p>The legacy data from Article 57 will be migrated to the ISO IDMP format as detailed in the following EMA webpage on '<a href="#">Implementation of the ISO IDMP standards</a>'.</p> |