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The launch of the new EudraVigilance System
Questions and Answers (Q&A) from stakeholders

Version 1.2

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Glossary

Acronym	Definition
ACK / NACK	Acknowledgment / Negative Acknowledgment
ARISg	Aris Global (web-based adverse event software)
ATU	Autorisation 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

Acronym	Definition
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 in preparation of the launch of the new EudraVigilance System, which is to go-live on 22 November 2017.

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

The document will be 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	Can an individual only be registered under one Organisation Identifier (ID)?	In accordance with the already established process, a user can be registered with several organisations, which are characterised by their organisation ID in EudraVigilance. The user 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.
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" of the XEVMPD/Art.57 database 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 MAH holds marketing authorisations in the EEA.
1.4	Does the current registration process change for access to XEVMPD and where is the online application for updating the XEVMPD data?	There is no change to the current registration process for submitting information on medicinal products to the Extended EudraVigilance Medicinal Product Dictionary (XEVMPD)/Art.57 database. 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 9 See also EMA webpage on 'Implementation of the ISO IDMP standards'). The XEVMPD will be maintained until that time and the URL is: https://eudravigilance.ema.europa.eu/X/?6

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 will continuously monitor 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?	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.

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 are 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 rest solely with the authorised representative of the MAH. |
| 1.7 | What happens if a MAH misses the allocated EVDAS registration timeslot? If we as MAH don't get access we might face challenges in being compliant by November in accessing EVDAS. What are the implications and contingency provisions?

Are there any rules for allowing changes to registered EVDAS users given that for many MAHs, the final business process may not be in place by November 2017? | The list of allocated timeslots for MAHs to register EVDAS users has been published by the Agency in May. As of 1 June the EVDAS user registration has been initiated and the MAH has a window of one month to perform their EVDAS user registration.

If an MAH misses the allocated registration timeslot, registration requests will be processed as soon as possible following receipt of the delayed request However, EMA cannot guarantee a specific timeframe.

Where changes to registered EVDAS users are required, the EU QPPV should inform the EudraVigilance Team and the request will be processed as soon as possible. |

Ref.	Question	Answer
1.8	What is the difference in the administrative and scientific profile of EVDAS users?	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.
	Can a MAH have five registered users for each profile?	
	What is the rationale for the limitation in users?	Users with and 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.
	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.	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 will continuously monitor 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.
1.9	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?	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).
		The overall responsibility for EudraVigilance access and user registration remains with the EU QPPV (company A).

Ref.	Question	Answer
1.10	If a EU QPPV registers users with a scientific profile, does the EU QPPV also need to register these users with EVWEB so they can access individual cases from the individual case line listing?	If an EU QPPV registers EVDAS users with a scientific profile, the EU QPPV does not need to register these users with EVWEB so they can access individual cases via the individual case line listing. The EVDAS Scientific profile in itself provides access to individual cases via the ICSR form directly from the individual case line listing. EVDAS users with the scientific profile do not need to be registered in addition with EVWEB.
		Note that the EVWEB and EVDAS registration processes are separate processes and are not linked. Registering a user with an EVDAS scientific profile does not add the EVWEB profile to create/send ICSRs.
		To register users for EVDAS, the EU QPPV has to register the user via the secure area of the EudraVigilance web page. The EVWEB Profile to create/send ICSRs can then be chosen in addition to the EVDAS scientific role if the user also performs these activities.
1.11	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 that they use for Eudralink or for the Service Desk. Within EVDAS, if users require access to the ICSR forms, they need to use their EudraVigilance login details.
1.12	How long it will take since EVDAS access is requested by a MAH user and EMA provide access?	EVDAS access is provided within 25 working days. Please note that access to EVDAS is not live until 22 November 2017 but the initial EV password must be used and changed within 30 days of receipt.

Ref.	Question	Answer
1.13	With the release of EVDAS functionality in November 2017, we would like to ask about registration for service providers / CROs. May MAHs outsource their signal detection activities; therefore it is important that these service providers / CROs have adequate access to the EVDAS system in November. Will a service provider be able to gain access to the system independently to perform signal screening for multiple MAHs? 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?	The obligation related to the monitoring of EudraVigilance is placed on the marketing authorisation holder 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)] The legislation does not foresee access to EudraVigilance data by service providers or CROs. However, CROs and IT vendors may be registered by a marketing authorisation holder, applicant, commercial or non-commercial sponsor as a third party service provider acting on behalf of these organisations by providing services related to EudraVigilance. It is for the MAH to define how they organise the monitoring of the data available in the EudraVigilance database. EVDAS registrations are to be managed 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.

Ref.	Question	Answer
1.14 **(new)**	Regarding the role of the EUQPPV. Is it possible for an affiliate to have its own EUQPPV, and in this case, does he endorse all the responsibilities for the affiliate pharmacovigilance system, or is the EUQPPV of the headquarters still responsible?	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. 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. 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. 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. Please find following the link regarding the "Information on the Member States requirement for the nomination of a pharmacovigilance (PhV) contact person at national level" http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/02/WC500221474.pdf. 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.

Ref.	Question	Answer
1.15 **(new)**	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?	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 • EudraVigilance: How to register • EudraVigilance: Testing process

2. Use of EVWEB and the ICSR download manager

Ref.	Question	Answer
2.1	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 will include all ICSRs for medicinal products registered by the MAH in the EVXMPD. Based on this, is it correct that MAHs won't be getting cases where another MAHs medicinal product name is reported.	The download function is based on the EudraVigilance Access Policy L2A. *Access is based on the active substance* for medicinal products, for which a 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. Downloaded ICSRs contain information on the medicinal product (trade) name as reported by the primary source, which allow an MAH to determine ownership of the medicinal product. Please refer to slide 62 onwards of the EudraVigilance Access Policy eLearning material (http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/06/WC500209351.pdf) and 36:55 of the eLearning video on EudraVigilance Access Policy: https://www.youtube.com/watch?v=WfuogTpCFWM&feature=youtu.be
2.2	Will only valid ICSRs be available for download?	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 will be further processed in EudraVigilance. Please refer to slide 22 of the EudraVigilance Access Policy presentation (http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/06/WC500209351.pdf) and 10:35 of the eLearning video on EudraVigilance Access Policy: (https://www.youtube.com/watch?v=WfuogTpCFWM&feature=youtu.be)

Ref.	Question	Answer
2.3	What clock start date should an MAH use (e.g. for onward sending outside the EEA)? Will this be defined by the EMA or left to MAHs to decide i.e. based on download date as per MLM?	The pharmacovigilance legislation does not define a "day zero" for ICSRs accessed via EudraVigilance by MAHs. 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. For reporting obligations outside the EEA, MAHs need to consult with the respective regulatory authorities and their requirements. For MLM ICSRs, the following was 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.
2.4	Will ICSR messages retrieved from EVWEB contain local language content?	ICSRs will be 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"?	The ICSR download functionality uses the date that the ICSR's 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. 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.
2.6	Is a user's login ID connected to an Organisation ID (Org Id) to obtain a list of "Active Substances" associated with that Organisation's ID?	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. Only user's registered at Headquarter level will be able to make L2 access requests.
2.7	Large organisations will 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?	The current ICSR export tool does not distinguish between serious and non-serious ICSRs. Note that seriousness in E2B(R3) format is assigned at reaction level. The download manager allows ICSRs to be downloaded in accordance with L2A\L2B access as outlined in the EudraVigilance Access Policy (revision 3). The downloaded ICSRs will then provide information on the seriousness of the cases.

Ref.	Question	Answer
2.8	How can a MAH determine if an E2B(R3) ICSR is serious before loading it into our database?	The following two options might be considered: **Option 1:** You can use the EU BFC tool and create an E2B(R2) format of the ICSR. The seriousness criteria at case level for the E2B(R2) format will be set automatically. However, a quality control should be put in place to validate the conversion. **Option 2:** The following XPATH statement can be used 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". 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'])
2.9	Will a MAH have access to reports for the same active substance submitted by a third party company?	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.

Ref.	Question	Answer
2.10	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 it seems we might not be able to download these cases from EudraVigilance because we would not have an entry in XEVMPD (I think) for the product prior to approval, and so cases would not be available to us for download. Currently we would/should (although probably not consistently) receive the cases directly from the local health authority.	For unapproved medicinal products for which there is no record in the XEVMPD, which is used to determine the substance based access in EudraVigilance, it is not possible to establish, which company should have L2A access. The cases are accessible via level 1 access and the MAH would need to screen the line listings to identify cases which might relate to the compassionate use programme. 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 their product into the XEVMPD.
2.11	Is it possible to designate a third party to perform the download of ICSRs?	A 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 will be able to perform the download of ICSRs associated with that MAH.

Ref.	Question	Answer
2.12	When an MAH submits a change to the XEVMPD, what is the timeframe for the change to be reflected in the EVWEB download tool? 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?	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. The ICSR download is possible the day after a new XEVMPD submission is marked as 'Validated by EMA' (up to a week from submission date, provided that the required information is suitable for validation). 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). The access to ICSRs is not time restricted so the export of ICSRs received prior to the new XEVMPD entry is also supported.
2.13	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?	The archiving of each download request will be performed after 30 days. The ICSRs remain available for download if the MAH makes another request.
2.14	When an MAH submits an ICSR to the EMA, will that ICSR also appear for download in EVWEB? Is there a way to filter these cases out?	The ICSR download function automatically excludes same sender ICSRs from the download.

Ref.	Question	Answer
2.15	Are users restricted to see the downloads that they have requested for themselves? 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?	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.
2.16	For what time period is archived downloads available for retrieval?	The results of download requests in EVWEB are saved for 30 days.
2.17	Will local NCAs also be reporting non-serious cases to EudraVigilance? Can a MAH expect non-serious cases from NCAs to also be available for export from EVWEB?	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: _table below_ ICSR downloads include both serious and non-serious as per the above reporting requirements (see also the EudraVigilance Access Policy revision 3).

Origin	Adverse reaction type	Time frame
Marketing authorisation holders		
EU	**All serious**	**15 days**
	All non-serious	**90 days**
Non-EU	**All serious**	**15 days**
Competent authorities in Member States		
EU	**All serious**	**15 days**
	All non-serious	**90 days**

Ref.	Question	Answer
2.18	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?	Apart from L2B requests (ICSRs including case narratives), ICSRs exported by an MAH are not tracked.
2.19	When EU assessment is present, will two assessments by the reporter and the MAH, be also present or not?	In accordance with the specific data elements as defined in the EudraVigilance Access Policy (revision 3), the information as provided by the sender, will be provided in the ICSRs exported.
2.20	The published material by the EMA states that an overview of duplicate masters with their linked duplicates can be made available to an MAH. Can you please provide details on how we can obtain/request this overview and what details it provides?	The "Master" ICSR (mastericsr) cases are included as part of the ICSR download in EVWEB. The "Master" includes a reference to the associated duplicates using the world-wide unique case identifiers of the duplicates. In addition, an EVDAS query which will show MAHs which of their cases are under a master is being developed and will be released after November 2017. The EMA will communicate closer to the time when it will be released. For technical details related to the specifications of master cases, please refer to the EU ICH E2B(R3) ICSR Implementation Guide.
2.21	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?	Nullification ICSRs are included for both masters and non-masters. Master cases can only be nullified by the EMA, and once they are nullified, the underlying duplicates will be reclassified so that they are no longer grouped together.

Ref.	Question	Answer
2.22	For stakeholder group III, access level 2B, will there be a difference in access based on which level the individual cases are coded (substance vs product)? Example: Company A, Product A, substance Paracetamol Company B, Product B, substance Paracetamol 1: If a case is coded on Product A, can Company B get access to level 2a data? 2: If yes to 1, then can Company B get access to all level 2b data (after formal request)? 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)?	Both EVWEB and EVDAS will provide access to MAHs at the level of the substance using the highest level in the hierarchy of the XEVMPD. This is known as the 'Active substance high level'. 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 coded as suspect/interacting and this is regardless of the product and regardless of the sender of the ICSRs. For the examples on paracetamol, both companies A and B will have access to level 2A and 2B for the cases where paracetamol is coded as suspect/interacting. Moreover, Company A will have level 3 access for the cases they have sent and Company B will have level 3 access for the cases they have sent. For the MLM cases, company A and B will get also level 3 access. Please note that the level 2B 'request' is automated in the system (EVWEB). Companies will 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.

Ref.	Question	Answer
2.23	Will 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?	ICSR export function will exclude all the ICSRs submitted by their own organisation. It will however include all ICSRs submitted by any other organisation that matches the active substances for which they hold an EEA MA.
2.24	Once we have submitted in EVWEB using manual data entry, will the submission be 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?	EVWEB will create E2B(R3) messages only. If you then implement a pharmacovigilance system that only supports E2B(R2) submissions this will mean that follow-up submissions will be in the less well-structured E2B(R2) format. Organisations are requested not to do this as this reduces the quality of the information between versions of an ICSR
2.25	Which active substances / products' information will we be able to access as MAH in the Levels 1 / 2A / 2B / 3?	The details of what information will be displayed at Level 1 and Level 2 are described in the EudraVigilance Access policy http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500218300 As a quick summary: Level 3 gives full access to the information as submitted Level 2 gives the verbatum substance and product information even if un-recoded Level 1 gives access to the product name for CAPs and substance name for products authorised through other procedures and will give no access to unclassified product and substance information e-Learning course is here: https://www.youtube.com/watch?v=WfuogTpCFWM&feature=youtu.be

Ref.	Question	Answer
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?)	Access to Level 2B is granted by the QPPV or deputy QPPV within your organisation. The following eLearning course shows how to make a Level 2B request: https://www.youtube.com/watch?v=huVGOfhx9Ug
2.27	Can you confirm that ICSR downloaded on active substance level will only include ICSRs sent to EMA by NCAs and not include ICSRs from other MAHs for the same active substance?	The EudraVigilance access Policy gives access to all EEA data regardless of the original sender.
2.28	Is the confidentiality agreement to access case narratives a one-time process or does it has to be signed for every request?	Each request requires the confirmation of the confidentiality undertaking.
2.29	Some EEA agencies have stated that they will be forwarding cases to EV in local language. Can you confirm that all data fields in EV will be in English with the exception of E.i.1.1a Reaction/Event as Reported by the Primary Source in Native Language and H.5.r Case Summary and Reporter's Comments in Native Language (the latter of which would not be available to MAHs anyway via EV download with level 2A access).	The ICSRs will be made available to MAH as reported to EudraVigilance and in line with the EudraVigilance Access policy

Ref.	Question	Answer
2.30	Is it possible to exclude ICSRs with other MAHs tradenames from ICSR download for a specific active substance?	No, the information is matched against active substances.
2.31	If a narrative is downloaded via L2B access is it allowed including this in the company safety database?	This is the choice of the MAH concerned; the MAH will need to ensure that EU data protection legislation is adhered to when storing this data in global systems.
2.32	Regarding EVWEB, Will it be possible to download the ICSRs by sorting according to country of occurrence?	A filter for Primary source country is available in EVWEB.
2.33	During ICSR Download from the EudraVigilance, will only products specific to the company of the person logged into EudraVigilance be downloaded if no other settings are selected?	The ICSR download is linked to the Organisation Headquarter ID, only users registered under the HQ can make L2 download requests and it will be for all products in the XEVMPD associated with that HQ.
2.34	Can you precise if nullflavor will be 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 nullflavor are permitted.
2.35	Will all elements not available for level 2.A users will be masked in ICSRs by Nullflavor?	In most situations the data elements will not be populated in the XML if no access is permitted. If a field is mandatory according to the XSD schema a nullflavor will be used.

Ref.	Question	Answer
2.36	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. Import into EVWEB? WebSpace? Is this part of EVWeb interface? So: export from EVWEB, import into WEBSpace and chose to see as RTF or HTML? Where can I find information on this?	E2B(R3) files can be imported into the EVWEB workspace and can then be printed in human readable formats. Please see the EVWEB user manual for more details: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500229855
2.37	Will ICSRs be re-routed as single ICSR messages only or can we expect to receive messages with multiple ICSRs?	ICSRs will be re-routed individually as single XML files.
2.38	Will EMA follow-up on missing ACKs on re-routed ICSRs? Incl. after one or more resubmissions?	The EU Implementation Guide has been updated to capture the retries that will be attempted; the following is proposed: "NCAs should return acknowledgements for rerouted ICSRs within 48 hours of the initial receipt. If no acknowledgement is received within 48 hours, EudraVigilance will automatically resubmit the re-routed ICSRs." First submission is 48 hours; second attempt is 24 hours third attempt is 24 hours. If not it is 6 days before service desk contacts the NCA EudraVigilance will resubmit ICSRs up to a maximum of three attempts following the initial re-routing if no acknowledgement has been returned. After the maximum number of resubmissions has been reached, the NCA will be contacted to confirm if they are experiencing technical issues."

Ref.	Question	Answer
2.39	Will current MedDRA versions be accepted in the new XCOMP environment? And will XCOMP be updated with every MedDRA release?	Yes, current version and one previous version (20.0 and 19.1) and XCOMP will be updated with every MedDRA release.
2.40	How will MAHs be notified that an ICSR sent to EV is merged into a "master case"?	Master cases will be made available to MAHs through the download ICSRs function
2.41	Are the re-routing rules from EV to NCA considering transmission date or receipt date?	Re-routing is based on the primary-source country, further details are available in the EU Implementation guide: ttp://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500165979
2.42	Will an MAH be able to download an ICSR coming from an ATU program running in France concerning an Active substance not yet granted a licence but maybe reportable to FDA?	If a product does not have a valid marketing authorisation approved in the EEA access will not be provided according to the EudraVigilance access policy
2.43	What is the criteria allowing EMA to identify a MAH product? The Owner identifier/registration organisation ID? The MAH Code? The MAH Name?	Entries in the XEVMPD through the use of the field Owner HQ identifier are used to establish the link between the logged on user/organisation and what ICSRs they have L2 access.

Ref.	Question	Answer
2.44	If an MAH identifies case reports under the signal detection process, that requires access to the case narrative, they will be 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 (as per NCA case download)?	1) L2B requests require that the requester enters the worldwide case ID(s) for the ICSR(s) required, same sender (Level 3) ICSRs will be excluded from such requests as these WW case IDs should be in the requester's own database and therefore there is no need to request them.
		However, if the requester 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 requested can view the whole case without having to complete the reason for the request and data protection obligation form.
	If one or many of the ICSRs retrieved under level 2B access needs to be added to an MAH's own safety database (because the ADR was missing for example), are there any issues for adding the case narrative component from these ICSRs to the MAH's database ? (it is stipulated that for the NCA downloads, case narratives will be stripped out for PII considerations)	2) The MAHs will need to ensure that European Data protection obligations are applied to any European data made available to non-EEA regulatory bodies or other organisations
	If it is a missing ICSR that requires submitting to other non-EEA Regulatory Agencies and/or Licence partners, we may end exposing the original case narrative downloaded from EudraVigilance – does the Agency have any concerns on this action?	

Ref.	Question	Answer
2.45	If we see that upon download not all ICSRs get created as R3 ICSRs upon creation – what action should an MAH undertake to report this issue to EMA given we are not able to identify the specific ADR (NB. I did see this during the pilot testing)	The ICSR download function automatically excludes same sender (L3) ICSRs from the download.
2.46	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.
2.47	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. User access permissions are manage by the EU QPPV/Deputy QPPV through the secure area of EudraVigilance under "manage your profile"
2.48	The agency cases that the MAH will retrieve in EudraVigilance will have their narrative in English? Or in the local language of the case?	The EMA will not be translating any cases. The narrative, which is only available with level 2B access or for MLM cases, will be in whatever language it was sent to EudraVigilance. MLM cases always have the narrative in English.

Ref.	Question	Answer
2.49	In relation to the search of cases in EVWEB using the new system. We would appreciate some guidance on the following scenario: a MAH had recently obtained an approval for a new indication with the corresponding new dosing and dosage form. The active substance that has already been approved some time ago. Therefore, it is possible that performing a cases search only using the name of the active substance, it will return on an elevated number ICSR items and most of them not applicable for the referred new indication/medicinal product. Please clarify if it would be possible to narrow this "active substance search" with the help of the following filters as "indication for use" and/or "new dosage form" and "dosing" characteristics in order to make a difference in reference to the rest of medicinal products containing the same "active substance"?	The download function is based on the EudraVigilance Access Policy L2A. Access is based on the active substance for medicinal products, for which a MAH holds a marketing authorisation. The dosage form field in ICSRs is currently a free text field and therefore a filter would be an unreliable way of identifying specific products. The indication stated on ICSR is captured as reported by the primary source which may not match the MedDRA terms of licenced indication; it is also therefore unreliable to trust as a filter. The country of the primary source can however be used to exclude countries where a product is not available on the market, however it should be noted that a patient is still able to obtain medicinal products by crossing borders.

Ref.	Question	Answer
2.50	Which format are Narratives downloaded? Excel, Word, XML?	The narratives will be exported in E2B(R3) format
2.51	If I understand correctly, EMA is no more re-routing ICSRs from NCAs to MAHs. If MAH is going to retrieve the ICSRs sent to EV from all NCAs, will it be still mandatory to send ACKs messages?	MAHs should not send acknowledgements for ICSRs downloaded from EudraVigilance
2.52	If case was submitted to a NCA prior to 22 November 2017 and needs to be nullified after 22 Nov, should the nullification be sent to the EMA?	For post-authorisation ICSRs the nullification should be sent to EudraVigilance, for clinical trial cases previously sent to an NCA the nullification should be sent to the NCA
2.53	Currently, we receive the cases by brand name from Health Authorities (i.e. Spanish Health Authorities). From 22-Nov-2017, we should upload the cases from EudraVigilance. If the brand name is not mentioned in these cases, should we assume that we are the owner of these products?	Yes, if there is no brand name mentioned in a case & you market the product in that territory, then you cannot exclude ownership & should assume that the case may be related to your product.

Ref.	Question	Answer
2.54	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?	ICSR forms level 1 and 2a do not contain the narrative. The narratives are provided in the ICSR form level 3 and in level 2b access in EVWEB. For more information about the ICSR form, please consults the ICSR form manual http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/06/WC500229803.pdf
2.55	Is it possible to copy & paste WWID's from the line listing (EVDAS) where case narratives are not visible and thereby need to be requested under level 2b from EVWEB?	It is possible to copy and paste WW case IDs one by one, delimiters need to be used when pasting a list of case IDs. Further guidance will be provided in the near future.
2.56	Will the EVWEB view in production open in internet explorer?	The supported browsers to be used to access EVWEB in production as of November 2017 will be: Google Chrome, Internet explorer and Mozilla Firefox.
2.57	Is there a limitation of numbers that the QPPV can designate to have Level 2b access from the EV registration screen? Is this number separate to those people registered as EVDAS scientific role?	There is no limit for the number of users the QPPV can designate to have level 2b access, it is just a user permission. This is a separate permission for the EVWEB interface only; it has no connection to EVDAS roles.
2.58	Please confirm the pre-requisite that a person NOT registered for EVDAS scientific can still have Level 2b access providing they are registered in EV at HQ level?	This is a separate permission for the EVWEB interface only and requires that the user is registered at HQ level

Ref.	Question	Answer
2.59	How will this 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?	The individual user that has been granted L2B access by the QPPV will themselves have to agree to the confidentiality undertaking and also provide the reason for the request
2.60	In tests files loaded from EVWEB test module there is no batch number (N.1.2) available and the date of batch transmission (N.1.5) is masked by a nullflavor, so they had to be manually added into the files in order to be processed in the database. Will it be the same in production environment?	The access policy does not give access to these fields of the original data, therefore they are currently not provided. This request is being reviewed and the generation of automated text to populate these fields is being planned to support the upload process by MAHs.
2.61 **(new)**	A list of all Master cases will be published by EudraVigilance/EMA. Where can we find the list of Master cases?	Each master case contains the case number & Safety Report ID of all of the underlying duplicates, in the "Other case identifiers" section (ICH E2B(R3) C.1.9.1). 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). You will be able to use this information to track which masters contain your cases. You will also be able to see from line listings for a given drug-reaction combination which of your cases are not present when a master case is.

Ref.	Question	Answer
2.62 **(new)**	Is there a character limit to the filters for companies that are responsible for over ~1000 products?	There is an effective limit of approximately 1,400 substance combinations. The exact number may depend on how many substances there are in each combination. Users should be aware that the larger the filter the longer it will take to run, therefore we recommend that, where possible, you limit your filters to no more than 500 substance combinations.
2.63 **(new)**	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?	This is being discussed internally by ANSM and the outcome of the discussion will be reflected as part of future updates of the Q&As related to the implementation of the new EudraVigilance system.

Ref.	Question	Answer
2.64 **(new)**	PV responsible person oversight specific to Germany. 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? 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.	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. 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. As long as the delegation is documented in writing and there is an appropriate oversight mechanism in place this practice is acceptable to us. 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.

Ref.	Question	Answer
2.65 **(new)**	What are the MAHs obligations regarding downloading of ICSR from EudraVigilance by MAHs: 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? What is the expectation if a downloaded ICSR contains the MAH product name as a subsequent suspected product?	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 the MAH 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 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. 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 a NCA or a MAH in the EEA. 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.

Ref.	Question	Answer
2.66 **(new)**	Is there a guidance document available or planned regarding the download functionality from EV Web, specifically, the filter functionality? Is a list of active substance group definitions which can be used for filtering available prior to the implementation of the new EudraVigilance system? Please provide an up-to-date status regarding the overall implementation (schedule) for the new CTR (milestones, timelines).	An eLearning course and a user manual are published on the EMA website. Please see chapter *2.11.3. ICSR Download* of the user manual for more information on the filters available EV Reporting process for users: Export functions in EVWEB (EV-M3c) EudraVigilance EVWEB User Manual The list of active substance groups associated with a specific MAH's organisation ID can be requested by submitting a service desk query. Please include the MAH Headquarter ID you are requesting for: https://servicedesk.ema.europa.eu
2.67 **(new)**	Will it be still possible to send XML in R2 format using the "IMPORT" option in EVWEB for Web Trader users? If yes, will some additional amendments need to be done to XML prior sending?	Yes, E2B(R2) ICSRs can be imported into EVWEB through the use of the workspace area. From the workspace the ICSR can be moved into the "create and send area" of EVWEB, by selecting the follow-up option. However, by doing this the ICSR will be converted into the E2B(R3) format and additional fields may need to be completed before sending, in order to comply with the E2B(R3) business rules.
2.68 **(new)**	XCOMP environment was made available in June, is it correct that E2B(R2) XML cannot be sent through testing environment?	The XCOMP environment accepts both E2B(R2) and E2B(R3) ICSRs. These can be sent by means of the EudraVigilance Gateway or the EV post function.

Ref.	Question	Answer
2.69 **(new)**	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 testing by clients is not required as long as the same version of software and configuration files are being used. If customisations are made then additional testing may be required.
2.70 **(new)**	Where can the QPPV request Level2b access for users?	The Level 2B access can be granted by the registered QPPV or deputy responsible for EudraVigilance, this done through the restricted area of EudraVigilance where user profiles are managed. The Manage Profile function is restricted in use to the responsible person and/or deputy administrator(s) of a Headquarter Organisation. To manage your profile, click Manage your profile from the main menu Next select the user that you wish to grant L2B access: Next select the user that you wish to grant L2B access: Select edit user: Tick the "Enable L2B Access" and then press the "update" button. Detailed process can be found in "EudraVigilance: Registration User Management": http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/06/WC500208955.pdf

Ref.	Question	Answer
2.71 **(new)**	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 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?	Users associated with affiliate organisations cannot see L2 data, they will only be able to see data sent by the affiliate. Users registered at the HQ level will be able to see all data including L2 data.
2.72 **(new)**	It is our understanding that narratives will not be available as standard from EudraVigilance Download Area for cases transferred to us from the NCA within EEA. Is this correct? If yes, what is the rationale for this? Today we receive the whole case directly from NCA, which allow us to perform proper evaluation of the case.	It is correct that case narratives are not part of the normal L2A ICSR downloads. The EudraVigilance access policy sets out the fields and rationale for access to fields such as the case narrative. Please refer to: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000674.jsp
2.73 **(new)**	When cases are downloaded from EVWEB what will be present in the receiver ID tag? Will it be the company downloading the ICSR?	The receiver ID will be set to the organisation ID of the user logged into EVWEB.

Ref.	Question	Answer
2.74 **(new)**	With regard to CT SUSAR reporting can EMA clarify whether reports sent to NCAs will be processed first by EV (generating acknowledgement) and then forwarded to NCAs or simply forwarded by the EV gateway?	The current SUSAR reporting process will not change until the application of the Clinical Trial Regulation. If the NCA is listed as the recipient, the ICSR or SUSAR is sent to the NCA directly through the gateway. The Acknowledgments will be generated by the NCA and returned via the gateway to the sender of the ICSR or SUSAR.
2.75 **(new)**	Will detailed training with print screens on EVDAS and ICSR downloading be made available?	Very detailed training on EVDAS for MAHs has been available since January 2017. EVDAS training for Marketing Authorisation Holders (EV-M5b). An EVDAS manual is under development. An eLearning course and a user manual have been published on the EMA website for downloading ICSRs. Please see chapter *2.11.3. ICSR Download* of the user manual for more information: EV Reporting process for users: Export functions in EVWEB (EV-M3c) EudraVigilance EVWEB User Manual
2.76 **(new)**	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?	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. You will need to take this into account as part of your arrangements with your licensing partners.

Ref.	Question	Answer
2.77 **(new)**	Case download The download function in EVWEB is based on the active substance of products, for which a MAH holds a marketing authorisation. To avoid missing of ICSRs is there any mechanism for the MAH to confirm/verify the access level and the filter assigned by EMA to download reports?	The list of active substance groups associated with a specific MAH's headquarter organisation ID can be requested by submitting a service desk query. Please include the MAH Headquarter ID you are requesting for in the query: https://servicedesk.ema.europa.eu
2.78 **(new)**	Case handling and contents: How will 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. If different organisations have previously sent the report to EudraVigilance, they will be combined under a master case.

Ref.	Question	Answer
2.79 **(new)**	Case handling and contents: What are the expectations for NULL flavours when sending reports to EMA, where follow-up was not possible? Will "NASK" be acceptable and not be interpreted as a failure to perform due diligence?	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.

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.

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 source confirms that the information is not available, the applicable nullflavor (ASKU) is also to be submitted as follow-up.

For reference please also see :

GVP 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."

And GVP VI Rev 2 Chapter VI.B.7.3, Amendment report:
"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."

For further information on the use of nullflavor refer to the EU ICSR Implementation Guide (chapter *I.C.3.7 Usage of nullflavor flags*)

If follow-up cannot be made UNK will be appropriate.

NASK can be used if no attempt at follow-up has been made. |

Ref.	Question	Answer
2.80 **(new)**	Submission requirements: Where shall nullifications for cases originally submitted to NCAs been submitted to? To EMA, or to the original destinations? If to EMA, how would that be possible if no previous case version had been sent there by the MAH?	The new classification of EEA nullification request has been added in order to allow MAHs to submit nullifications for cases previously sent to NCAs. Please see the EU implementation guide for further details. Please refer to: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/04/WC500165979.pdf
2.81 **(new)**	Submission requirements: How will the submission of downgrade reports be 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.
2.82 **(new)**	EVWEB ICSR download Will EMA publish only ICSR for download from the EEA (or also from other countries/regions)? The recent Q&A does not address this question and stakeholders are concerned that outside EEA cases will be made available for download.	The download ICSR function is for EEA cases only. MAHs will also have access to all worldwide data in EudraVigilance through the ICSR search function and EVDAS in support of their pharmacovigilance obligations including signal management.

Ref.	Question	Answer
2.83 **(new)**	Regarding the ICSRs reported by the NCAs Could you please give us more details regarding ICSR download functionality of EVWEB (other than data described in the document EudraVigilance stakeholder change management plan) ? Is it a new tool of EVWEB ? What will be the mandatory frequency for downloading the cases ?	The download function is part of EVWEB, an eLearning course and a user manual have been published on the EMA website. Please see chapter *2.11.3. ICSR Download* of the user manual for more information EudraVigilance training page link EV Reporting process for users: Export functions in EVWEB (EV-M3c) EudraVigilance EVWEB User Manual 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 the MAH 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 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. 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 a NCA or a MAH in the EEA.

Ref.	Question	Answer
2.84 **(new)**	Regarding the registration for EVDAS Can a user of the affiliate have access to EVDAS? Will the list of substances covered by EVDAS be the same that the list of substances covered by MLM? When the list of substances covered by EVDAS will be published?	Only users at headquarter level can have access to EVDAS. The MLM service covers 300 substance and 100 herbal substance groups, whilst EVDAS will. 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. The EVDAS queries on substance groups covered by EVDAS will be made available in November at the time of the go-live of the new EV/EVDAS system.
2.85 **(new)**	Regarding XEVMPD Is it possible to have several EUQPPVs registered for the same account (ie. if an EUQPPV is registered for an affiliate, can the EUQPPV of the affiliate be selected while creating a new product in XEVMPD instead of the EUQPPV of the headquarters)? After the creation of an affiliate, will the affiliate have its own account to XEVMPD or will the affiliate share the same account as the headquarters?	The answer is yes, each MAH has the main QPPV at the headquarter level and also if there are any subsidiaries/affiliates, then each affiliates which holds MAH within the EEA has other local QPPV. If the affiliate is setup as web trader and sends the reports directly from the profile, then they have separate PV systems. Some affiliates are setup with transmission mode via headquarter, that means they are present at the database with separate ID and also EV code only for reference and all reporting is done from the headquarter level. There is another way how to appoint a QPPV, if there is specialized QPPV only for one product not related to any affiliate, then the QPPV is setup as a standard user with QPPV rights in the EV database. This QPPV is then a standard user under the headquarter with QPPV rights and can then be appointed to 1 or more products in the XEVMPD.

Ref.	Question	Answer
2.86 **(new)**	The EMA has recently acknowledged to some companies that their sample files had attachments that didn't meet the expected standards and therefore couldn't be downloaded/unattached. Will EMA be providing updated files and if so, when can they be expected?	The XCOMP system will be updated on the 21 September and the compression algorithm will be changed from RFC1950 to RFC1951. The test files will then be updated and republished accordingly.
2.87 **(new)**	Currently, NCA/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?	Technical solutions for MAHs for potential future automation are being investigated but currently there is no firm date for implementation of such solutions. For NCAs in the EEA, the messages are already automatically rerouted.
2.88 **(new)**	What is the process if a download from EVWeb fails?	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 EU ICSR Implementation Guide, which can be accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/04/WC500165979.pdf If you are having a specific technical issue you should contact the EMA service desk for support: https://servicedesk.ema.europa.eu
2.89 **(new)**	Please provide a sample R3 masterichicsr file	Some examples are already published on the EMA website as part of the testing files: EU E2B(R3) testing files

Ref.	Question	Answer
2.90 **(new)**	Please provide sample R3 test files that contain more data. The sample files on the EudraVigilance site have only a few fields populated. We would like to see sample files that are more fully loaded with data populated to test our BFC mappings and business logic.	Organizations are encouraged use EVWEB in the XCOMP environment to create their own E2B(R3) test files which can be further utilized to perform backwards and forwards conversion testing.
2.91 **(new)**	Signal detection activities. When an MAH is deleting products, will this impact the expected process for signal detection in EV? Will, once a product is deleted, the signal detection requirements (periodicity) change? Please provide information on how long signal detection activities will be required and the frequency, post product deletion.	The legislation does not require MAHs to monitor EV data for withdrawn medicinal products. XEVMPD entries can only be marked as withdrawn; they cannot be deleted as such. The changing of status of XEVMPD does not lead to ICSR data being changed. If all products containing the same active substance are marked as withdrawn by an MAH, that MAH will no longer have L2A/B access to ICSRs referring to that active substance.

Ref.	Question	Answer
2.92 **(new)**	How re-coding of drugs on cases are distributed and how will this be used across EU (EMA, Industry, NCAs); will MAH be able to download cases with original coding as well as EMA re-coded cases? As far as we are aware, EMA re-coded cases will not be distributed to NCAs (?). Example: We, as an NCA have experienced that when we submit a case coded on different products to different MAHs, then they return these cases coded on substance for products they do not have in their database.	The EU Implementation guide explains how the drug names will be classified against the XEVMPD and how this will be provided in the E2B(R3) XML files. See sections I.C.6.2 Classification of Medicinal Product Information & I.C.6.2.1 Classification of medicinal products in the interim period before ISO IDMP is available. The rerouting of ICSRs to NCAs is performed without changing what was originally submitted. Once the ISO IDMP is implemented NCAs will be able to choose to receive updated ICSRs classified against the ISO IDMP set of standards.

3. Medical Literature Monitoring

Ref.	Question	Answer
3.1	Will the MLM list of substances stay the same or change?	The MLM list of substances monitored by the Agency remains unchanged.
3.2 **(updated)**	Presumably the access will still be linked to XEVMPD data. One of the eLearning videos said this would be updated each night—is that right?	All MAHs already have, and will continue to have, full access to all MLM cases for substances that the Agency is monitoring.
3.3	Can the MAH continue to use their XML filters to retrieve valid ICSRs?	The MAH will need to set up a new filter.
3.4 **(updated)**	It was specified in the module "Medical literature monitoring by EMA (EV-M7)", that we can access to the MLM cases either via Single case downloading, General bulk downloading, or MLM bulk downloading.: For the "Single case downloading", we have to enter the reference of the case in order to download a single MLM case. So normally we should be aware of the case previously? So, the query should be already done via ICSR download? So, what is the real interest of the "Single case downloading"? What is the interest of downloading MLM cases via General bulk downloading? We could download them via "MLM bulk downloading", in this way we will only have the MLM cases without the other cases that were submitted to the agency via HCP/patient. Could you please clarify this point?	Since different stakeholders have different requirements, the Agency is making various methods of accessing the MLM cases available. You will need to decide which method is most convenient for you. Since the Agency publishes daily MLM tracking sheets, MAHs can be aware of all transmitted MLM ICSRs if they wish to be and can therefore know which case numbers to search for.

Ref.	Question	Answer
3.5 **(new)**	How to create the product filter for MLM and modify them? Where will the filters be saved in the new system?	In the new EudraVigilance system the MLM downloading will be performed in EVWEB. Once you have created a filter you will be able to export it and store it locally as you do at present. You can already create a filter using the XCOMP version of EVWEB & from 9 October you will be able to validate it against a set of real data that matches a specific time period from production, to ensure that you are retrieving the same data that you do at present. The EMA will notify MLM Service users on 6 October which date range to compare the data in XCOMP against.
3.6 **(new)**	When should the posting of the user manual for the new MLM system be expected?	The new ICSR download functionality, which includes the MLM ICSRs, is detailed the updated EV User manual (pdf). The MLM user manual is scheduled for an update by 6 October 2017, to highlight various new MLM functionalities.

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?	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: "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)].
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?	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). 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. For further reference: GVP VI Chapter VI.B.7, Submission of individual case safety reports (ICSRs) states the following: "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."

Ref.	Question	Answer
4.3	If a follow-up is required by a MAH on a case that was submitted to EudraVigilance by an NCA, does the MAH follow-up directly with the NCA or with EudraVigilance?	GVP VI Rev 2 Chapter VI.C.2.2. Responsibilities of marketing authorisation holder in EU states the following: "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."

Ref.	Question	Answer
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? 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"?	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. For example, an ICSR should be submitted as amendment report to EudraVigilance with the applicable null flavour (UNK) where the information (e.g. batch number of a vaccine) was asked but the primary source did not respond to the request for information. 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 source confirms that the information is not available, the applicable nullflavor (ASKU) is also to be submitted as follow-up. For reference please also see : GVP 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."* And GVP VI Rev 2 Chapter VI.B.7.3, Amendment report: "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." For further information on the use of nullflavor refer to the [EU ICSR Implementation Guide](#) (chapter *I.C.3.7 Usage of nullflavor flags*).

Ref.	Question	Answer
4.5	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?	The ICSR should be created or updated in accordance with the data that has been initially provided and received. See question 4.4. 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. From GVP VI Chapter VI.C.6.2.2.7. Follow-up information: "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 necessitates medical judgement. (…)" For further details see also question 4.4.
4.6	What are the reporting and download rules of ICSRs after go-live of the new EV system for the below scenario?	Please refer to the answers as provided in Figure 1. Response to question ID 4.6.

Figure 1. Response to question ID 4.6

	Scenarios	ICSR reporting – current state	Simplified reporting – post 22 November 2017	EVWEB ICSR download
a)	Both companies have marketing authorisations in the EU and each handles their reporting.	Both partners report to the individual counties in the EU where they are the MAH; Scenarios for reporting to EudraVigilance: Partners both report to EudraVigilance for countries outside the EU or 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?) **Answer** - 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. In such situations where an agreement is in place one party can perform the reporting. 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? **Answer** - 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. 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.
a)	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? **Answer** - See above for scenario a)	As above **Answer** - See above for scenario a)

	Scenarios	ICSR reporting – current state	Simplified reporting – post 22 November 2017	EVWEB ICSR download
c)	One company reports on behalf of the partner which holds a EU marketing authorisation; note the company is not a MAH in any EU country	The company reports on behalf of the partner.	Can the organisation continue to report on behalf of the partner? **Answer** – 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. If this is not followed, the ICSRs will appear for EudraVigilance download by the MAH when they perform an export.	Partner as the MAH to access and download the ICSRs, or can we do that for them through delegation? **Answer** - 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.

Ref.	Question	Answer
4.7	Does the EMA require a deletion notification for a ICSR originally reported to a 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 a 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? 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.
4.9	We understand that cases exported from EV will not have narratives. 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. The EMA is not in a position to advice on non-EEA requirements for creating and provision of case narrative. 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
4.10 **(updated)**	Regarding Module VI: Amendment is a significant data clean up, with an initial receipt date equal to last significant information. Do amendments must be included into compliance metrics as for significant follow ups?	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. 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. 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. Information on compliance monitoring concerning amendment reports is provided in GVP VI chapter VI.C.6.2.2.8 (Amendment of cases): - 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 15 or 90 days submission time frames since the date of receipt of the most recent information should remain unchanged. - 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.

Ref.	Question	Answer
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?	Information is already provided in chapter VI.C.4 of GVP VI Rev 1.: 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. This is independently of the condition of use of the suspected medicinal product and of the expectedness of the adverse reaction. a. Serious ICSRs • 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. • 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. b. Non-Serious ICSRs • Marketing authorisation holders shall submit all non-serious ICSRs that occur in the EU to the EudraVigilance database only. • Competent authorities in Member States shall submit all non-serious ICSRs that occur in their territory to the EudraVigilance database.

Ref.	Question	Answer
4.12 **(new)**	When will the Clinical Trial Regulation (EC) 536/2014 and the simplified reporting of SUSARs directly to EVCTM be implemented?	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. The Regulation will become applicable six months after the European Commission publishes notice of this confirmation.

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.

The EMA's Management Board will discuss a new delivery time frame in October 2017 once the developer confirms progress.

Due to these delays, the EU Clinical Trial Regulation will come into application during 2019 instead of October 2018, as previously scheduled.

Information on the Clinical Trial Regulation 536/2014 and its implementation is provided on EMA website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp&mid=WC0b01ac05808768df |

Ref.	Question	Answer
4.13 **(new)**	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." The previous Module VI wording was "or". Is this a change in the requirements?	Reference is made to GVP VI chapters VI.A.1.5. (Medical confirmation). 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. 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.
4.14 **(new)**	What is the timeline for sending Literature articles or other attachments as amendments upon request?	Reference is made to GVP VI chapters VI.C.6.2.3.2. (Suspected adverse reaction reports 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, 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. MAHs should endeavour to provide the article within the requested timeframe and inform the requester if delay is envisaged.

Ref.	Question	Answer
4.15 **(new)**	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. _QUESTION FROM.Q&A:_ _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 a NCA?_ _ANSWER: 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 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_	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). 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). 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. 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. 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. *_'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.

Ref.	Question	Answer
4.16 **(new)**	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?. 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? Where, after EV Web downloading of cases, a translation is made how would the translation piece be submitted and added to the existing case? From the Q&A, answer to question 5.4: ["*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 …*"]	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). 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. 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. The ICSR should be completed and submitted in English if not otherwise requested. 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. ` 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. 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). Additional documents held by the sender, which may be only available in a local language, should only be translated if requested by the he Agency or another Member State. The updated ICSR should be submitted as amendment reports (see GVP VI Chapter VI.C.6.2.2.8. (Amendment of cases)).

Ref.	Question	Answer
4.17 **(new)**	Off-Label-Use (OLU). OLU in Named Patient Programs and Free Goods Provision: Are companies expected to collect OLU without AE when a product is provided off label in the context of NPP or free goods? And 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. 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 [...]	When a medicinal product is administered off-label in the frame of a named patient use/companionate use, the guidance provided in GVP VI chapters VI.C.1.2.2. should be followed: - For compassionate use and named patient use conducted in Member States (or in countries outside the EU) where the active collection of adverse events occurring in these programmes is required, 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. - For compassionate use and named patient use conducted in Member States (or in countries outside the EU) where the active collection of adverse events occurring in these programmes is not required, 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. When a medicinal product is administered off label in the frame 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. - 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).

Ref.	Question	Answer
		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.). 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.).

Ref.	Question	Answer
4.18 **(new)**	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. 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. Can EMA elaborate on this process and the types of items they will be looking for? Deadlines expected for corrective action? How frequently will these be provided to NCA/MAH? Are there repercussions to companies found with regular non-compliance? Will this begin upon 11/22 date of EV Go Live?	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). 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. 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. Parameters upon which the review of organisations may be initiated regarding ICSRs quality and integrity, refer for example to - the volume of reports being submitted to the EudraVigilance database, - major changes to pharmacovigilance databases, - quality issues identified as part of the signal management, - requests from pharmacovigilance inspectors, or - the time interval since the last review. 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. 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).

Ref.	Question	Answer
4.19 **(new)**	Duplicate searches. Can the EMA share information on the duplicate searches with MAH? What will it look like and what is expected from MAH?	MAHs are expected to review their databases for duplicate cases. You are not expected to actively review EV, as the EMA is doing this. Once duplicates are confirmed, they will be merged under a master case, which will be transmitted to EV & stakeholders will be able to download these. If you suspect duplicate cases in EV, please email the case numbers to duplicates@ema.europa.eu in accordance with the process described in GVP Module VI, Addendum 1. The EMA will be publishing information on our duplicate detection algorithm is performed in due course.

Ref.	Question	Answer
4.20 **(new)**	If possible, it would be beneficial to have a more detailed update/discussion/point to consider on how duplicates and Master cases are managed and what is not expected; How infinite loops of sending, updating and re-routing are avoided, especially when updates are circulated, incl. nullifications 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	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.

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.

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.

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.

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.

Nullifications DO count as significant updates and should be performed as usual. |

Ref.	Question	Answer
4.21 **(new)**	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?	In accordance with GVP Module VI, Adddendum 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 send an email to duplicates@ema.europa.eu with information on which cases are suspected to be duplicates. The Agency will not routinely send feedback on whether or not the cases are duplicates. To receive such feedback, the sender of the email should request this in the email. 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. 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:

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	

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.

These masters are then made available to organisations as part of the normal download process.

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.

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?	For the detailed legal provisions on the simplified reporting rules please refer to the [announcement of the EMA Management Board on the confirmation of full functionality of the EudraVigilance database](#) and GVP Module VI Chapter VI.C.2.1 (Responsibilities of Member States) which states the following:
		"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)].
		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."
		In addition, Article 107a, paragraph 4 states the following:
		"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".

Ref.	Question	Answer
5.2	With reference to question 3.1: What about local systems like PV Networks in Italy?	The Italian Medicines Agency will not receive any more the Italian ICSRs directly by the MAHs because they shall submit ICSRs to EudraVigilance in accordance with the provisions set out in Dir Art 107(3) and further detailed in VI.C.4." Suspected ADR reporting forms for healthcare professionals and consumers are available on the website of AIFA and a reporter can send the filled ADR reporting form directly to the Responsible of Pharmacovigilance (RPhV) of the local structure to which the reporter belongs. The reporter can find the addresses of the RPhV to this link http://www.agenziafarmaco.gov.it/it/responsabili. The RPhV is the user responsible for the data entry process in the National Pharmacovigilance Database (NPhVD) and after few days all cases (serious and non-serious) registered in the NPhVD are and will be automatically transmitted and uploaded in EV. The online reporting modality has also been made available to the public at this link www.vigifarmaco.it. Healthcare professionals and consumers may also report adverse events and/or medication errors to the MAHs. If a MAH receives an ADR report, it will have to transmit the report only to EV as specified by regulations. We think to leave the visibility of data in the NPhVD to the MAHs (only for their products) in order to handle the duplicates and/or follow-up.
5.3	Do Spanish non-serious cases require a Spanish narrative?	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)]. 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.

Ref.	Question	Answer
5.4	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? 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.	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. 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. 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. 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.

Ref.	Question	Answer
5.5 **(updated)**	Does the EMA expect that ICSRs provided by NCA to EMA be made available in English language in all E2B free text fields?	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. 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. 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.
5.6 **(updated)**	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 a NCA?	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)].

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

Ref.	Question	Answer
6.1	What is the frequency of signal detection using EudraVigilance?	Please refer to revision 1 of GVP IX, which is being finalised and will be published in advance of the go-live.
6.2	Are there recommendations for thresholds when a more detailed analysis/discussion should be done?	The eRMR provides the EudraVigilance data and the disproportionality analysis, but it does not state which DECs should be further analysed.
		MAHs should exercise scientific rationale when deciding which DECs from the eRMR deserve further analysis. This should be based on the knowledge of the safety profile of the medicinal product (including closely related terms that are labelled), exposure, patient population, previous assessments etc.
		Statistical signal detection has to be complemented with clinical and scientific assessment and judgement as a SDR is not the same as a validated signal and there could be real safety signals that do not show as SDRs (~ 50% of the signals raised from EV data did not appear as SDRs).
6.3	Are there specific criteria for a risk-based approach? Is it sufficient to search the EV database only for specific drugs/active substances for which in the own signal detection process (using global safety database) signals were detected?	Article 18 of the Commission Implementing Regulation 520/2012 states that MAHs, NCAs and the Agency shall ensure the continuous monitoring of the EudraVigilance database with a frequency proportionate to the identified risk, the potential risks and the need for additional information.
		The risk-based approach therefore applies to the frequency for monitoring EudraVigilance. Please also see question 6.1 'What is the frequency of signal detection using EudraVigilance?'
		Using EudraVigilance to consult specific Drug Event Combinations for signal strengthening cannot be considered a 'continuous monitoring' of the database.

Ref.	Question	Answer
6.4	An MAH with numerous well established medicinal products approved will want to perform signalling using EVDAS in a six-month interval for these products. To distribute the workload and to avoid reviewing all medicinal products in the same month, these reviews are intended to get scheduled in a way that an equal number of medicinal products get reviewed each month based on eRMRs for six-month periods. Is there an expectation that the first review for each medicinal product starts with an eRMR for a period starting with the same month, i.e. June 2017 or is it acceptable to use an eRMR starting with June 2017 for a medicinal product reviewed in December, an eRMR starting with July for a product reviewed in January, and so on?	The request for flexibility is acknowledged. Further guidance on practical aspects of transitional arrangements for MAHs will be published closer to the start of the new process.
6.5	Regarding the expectation for the MAH to screen product information within EU for signals already potentially addressed: where can the MAH will find this information?	Please refer to revision 1 of GVP IX, which is being finalised and will be published in advance of the go-live.

Ref.	Question	Answer
6.6	When the signal notifications form used for a standalone notification will be available for the MAH? What kind of information should be provided in this form?	The standalone signal notification form is being finalised together with GVP IX revision 1 and will be made available before the new process for MAHs starts.
6.7	For a combination product, do you expect us to screen the products individually and then screen the combination product?	When a combination of substances is considered a unique active substance high level, routine signal detection in EudraVigilance can be performed using the combination. Nevertheless, safety information for the single ingredients may be relevant during the analysis of safety data related to the combination so MAHs may take the opportunities provided in EV to retrieve the data for other active substances, including single ingredients used also in combinations.
6.8	Based on the information published on the European medicines web-portal (see IX.C.8.), the signal was not recently addressed by (a) competent authority (ies) of (a) Member State(s) or by PRAC. What do you mean by "Recently"?	Please refer to revision 1 of GVP IX, which is being finalised and will be published in advance of the go-live.
6.9	Do you plan to adapt/update the PBRER format according to the new process of SD (sections dealing with signals)?	The availability of EudraVigilance for MAHs and the new signal management process does not modify the format and the PSUR process. The PSUR should contain all validated signals for which the evaluation is finished or ongoing at the PSUR DLP. This is regardless of the source of the signal or the actions taken with the signal. Data from EudraVigilance should be considered when preparing the PSUR as another source of safety information. As stated in the GVP Module VII, PSURs shall be based on all available data.

Ref.	Question	Answer
6.10	Is it expected from MAHs of generic products to use eRMR/ EVDAS for signal detection and further tracking? OR EVDAS be used for validation only?	All MAHs without distinction shall monitor EudraVigilance data according to Commission Implementing Regulation (EU) No 520/2012. Please also refer to the information on transitional arrangements published on the Agency's signal management webpage: (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b)
6.11	From an NCA perspective, what is the average number of signals per eRMR? a) Statistical? b) Potential? c) Validated?	EMA publishes every year the Annual Report on EudraVigilance for the European Parliament, the Council and the Commission. The 2016 annual report can be retrieved in the following link: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/03/WC500224056.pdf The 2016 annual report states the following: "In 2016, the Agency's Signal Management Team reviewed in detail a total of 2,076 potential signals (i.e. drug-event pairs from screening of the EudraVigilance database, medical literature, information received from other regulatory authorities etc.) for substances included in centrally authorised medicinal products. Overall the major source of EMA potential signals in 2016 continues to be EudraVigilance, from which 82.7% of potential signals originated. The number of confirmed signals prioritised and assessed by the PRAC in 2016 was 94, compared with 102 in 2015. Of these 94 signals, 48 were validated by the Agency and 46 were validated by the MSs in the course of ongoing ADR reports monitoring through screening of reaction monitoring reports, ADR reports, medical literature and other safety data; overall 66% included data from EudraVigilance as their source." For further information on the EudraVigilance activities, please consult the 2016 annual report: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/03/WC500224056.pdf

Ref.	Question	Answer
6.12	Please clarify what is meant by TME?	TME is described in the guideline 'Screening for adverse reactions in EudraVigilance' published in Dec 2016: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218606.pdf
6.13	Can you please confirm that MAHs have a grace period between 22 Nov and 22 Feb to fully implement their processes around signal detection with EVDAS?	Please refer to the information published on the Agency's signal management webpage (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b)
6.14	Due to the enhanced collaboration between EMA and WHO, the EudraVigilance data will be included in VigiBase. Would it, therefore, be acceptable that the MAH monitors VigiBase instead of EudraVigilance to fulfil the request of monitoring EudraVigilance data?	Commission Implementing Regulation (EU) No 520/2012 explicitly requires that MAHs monitor the data available in EudraVigilance, not VigiBase. Of note, the transfer of data from EudraVigilance to VigiBase will only concern ADRs occurring in the EU and from 22 November 2017. The EudraVigilance access policy describes the levels of access for the different stakeholders. MAH can have access to level 2a (228 E2B data fields) and Level 2B (230 E2B data fields). WHO is provided with level 2C (134 E2B data fields).

Ref.	Question	Answer
6.15	Following publication of the EMA letter on the monitoring of the EudraVigilance database by marketing authorisation holders on 20-Jul-2017, could you please clarify whether for the one-year pilot period, all the MAHs of active EEA licenses for the active substances included in the 'List of medicinal products under additional monitoring' are required to monitor EudraVigilance and inform EMA/NCA of validated signals or whether this only applies for the MAHs of the products present in the 'List of medicinal products under additional monitoring' and for which the approved PI includes a black triangle?"	The pilot will concern all active substances included on the 'additional monitoring list' in force as of 22 November 2017. Please refer to the information published on the Agency's signal management webpage: (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b)
6.16	How many days after a standalone notification, PRAC informs the QPPV about a signal "non- confirmation" or "confirmation"?	Please refer to revision 1 of GVP IX, which is being finalised and will be published in advance of the go-live.
6.17	How should we obtain the originator's labelling for reviewing for signal detection purposes? Will there be guidance?	Please refer to revision 1 of GVP IX, which is being finalised and will be published in advance of the go-live.

Ref.	Question	Answer
6.18	Are MAHs expected to re-validate non-confirmed signals? If yes, should they be sent to PRAC through one of the communications routes?	Please refer to revision 1 of GVP IX, which is being finalised and will be published in advance of the go-live.
6.19	Can we have an example of the EPITT?	EPITT is database used by EMA and NCAs to track information on various pharmacovigilance processes including validated signals. Information on signals assessed by PRAC is published on the Agency's website.
6.20	Would you know when the Standalone Form will be published?	The standalone signal notification form is being finalised together with GVP IX revision 1 and will be made available before the new process for MAHs starts.
6.21	Will we be able to see the reason for non-confirming a signal in the report sent to the QPPV including the confirmed and non-confirmed signals?	Please refer to revision 1 of GVP IX, which is being finalised and will be published in advance of the go-live.
6.22	Have you identify which products will be included in the pilot phase in EVDAS	Please refer to the information published on the Agency's signal management webpage (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b).

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

Ref.	Question	Answer
7.1	Regarding the selection of the active substances to query the EVDAS reports, are MAHs able to select substances only for their own medicinal products?	No. MAHs can select any active substance to retrieve eRMRs and line listings from EVDAS. This access is based on Level 1 access according to the EudraVigilance Access Policy. Different levels of access depending on the product for which the MAHs hold a marketing authorisation is provided for the ICSR form. • ICSR form level 1 if the MAH does not have a product for the specific substance • ICSR form level 2a if the MAH has a product for the specific substance • ICSR form level 3 if the case has been previously submitted by the MAH and for the MLM cases. Access to EudraVigilance data in EVDAS for MAHs is provided at the level of the 'active substance high level', which is the highest grouping in the hierarchy of the XEVMPD.
7.2	Are MAHs able to view data in the EVDAS reports on only the MAH's product(s), or does the MAH view the data for all MAH's for the "active substance"?	Access to EudraVigilance data in EVDAS for MAHs is provided at the level of the 'active substance high level'. EudraVigilance 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. The eRMR and line listings are based on level 1 access according to the EudraVigilance Access Policy and the output-fields are the same regardless of the substance and regardless of the MAH querying the database. When retrieving ICSR forms from the link provided in the case line listing, different levels of access (level 1, 2A and 3) as per the EudraVigilance Access Policy are provided depending on the MAHs and the medicinal products for which they hold a marketing authorisation in the EEA. (See question 7.1) The case line listing and ICSR form provide the reference to the world-wide unique case identifier to facilitate case reconciliation within the MAHs databases where necessary.

Ref.	Question	Answer
7.3	Medicinal products are currently entered via an affiliate registration in our EudraVigilance set-up. For the purpose of retrieval of safety information from EudraVigilance, do the medicinal products automatically roll-up to the headquarter ID for an MAH?	The users registered with the headquarter organisation ID can have L2A/B access as this is based on the XEVMPD data, which is linked to a headquarter organisation ID. Affiliates therefore can only have L1 or L3 access.
7.4	Can MAH users of EVDAS retrieve data for multiple active substances at the same time?	EVDAS users can select different active substances at the same time to retrieve data when using the fixed reference period eRMR, the line listing and the active substance grouping reports. The ad-hoc reference period eRMR only allows for the selection of one substance each time the report is run; this is to protect the performance of the system.
7.5	Can the users filter the data in EVDAS using MedDRA?	The MedDRA hierarchy including SMQs level 1 broad and narrow can be used to filter the data in the eRMRs and in the case line listings. The MedDRA prompt is not mandatory.
7.6	Which one is the best eRMR report to use when monitoring substances every two weeks?	The eRMR allows for the continuous monitoring of the EudraVigilance database. For the best use of the eRMR, the frequency of monitoring should be in line with the eRMR reporting period, as the eRMR will highlight the new cases since the last review. To monitor substances every 2 weeks, the ad-hoc reference period eRMR report should be used. This report allows for the selection of the reporting period between 1 to 105 days. On the contrary, the fixed reference period eRMR is designed to monitor the substances every 6 months as this eRMR contains a default reference period of 6 months.

Ref.	Question	Answer
7.7	Does the line listing retrieved from the hyperlink in the number of cases in the eRMR contain always the same cases as stated in the eRMR, even if the line listing is retrieved on a different day?	Users should always take into account that EVDAS is updated every night. The hyperlinks in the eRMR to retrieve the case line listings work even if the eRMR has been exported in Excel/PDF. By clicking on the hyperlinks, EVDAS runs the line listings 'in situ' and provides the data according to the most updated information in EVDAS. Therefore if users retrieve eRMRs and line listings on different dates, the number of cases may be different (e.g. if nullification and de-duplications have occurred).
7.8	When calculating the Reporting Odds Ratio (ROR) in the eRMR, is the type of product (e.g. vaccines) taken into consideration for the calculations?	The ROR is provided for each of the drug-event combinations in the eRMR and does not take the type of medicinal products into account for the calculation. The ROR is calculated using as background parameters all the medicinal products and all the spontaneous suspected reactions reported to the EVPM. Reports from studies (observational from the EVPM and interventional clinical trials from EVCTM) are not included in the calculation of the ROR. The calculation of the ROR is described in the guideline 'screening of adverse reactions in EudraVigilance'.
7.9	Are the RORs for special populations calculated on all active substances?	The fields provided in the eRMR are stable and the output contains always the same elements regardless of the substance. Statistical calculations of the ROR for paediatrics and geriatrics are always provided in the eRMR; this is per drug-even combination providing that ICSRs have been submitted within these populations to support the calculations. Statistical calculations of the ROR for special populations are described in the guideline 'screening of adverse reactions in EudraVigilance'.

Ref.	Question	Answer
7.10	What type of drug-event combinations MAHs should further analyse and review following the screening of the eRMR? Is the expectation that MAHs will always review special population statistics? Or products with no paediatric indication should paediatric SDRs be further analysed?	Statistical signal detection should always be combined with medical and clinical judgment and input. MAHs should decide which drug-event combinations should be further evaluated following the screening of the eRMR. This decision should be based, amongst others, on the knowledge of the medicinal product, identified risks, potential risks and missing information. GVP IX, GVP Addendum I and the guideline on 'screening for adverse reactions in EudraVigilance' provide general principles for signal detection. Regarding the SDRs for special populations, EVDAS calculates the relative RORs using the age reported in the ICSRs. SDRs in the paediatric population for medicinal products/substances without a paediatric indication may be highlighting safety issues related to the off-label use of the medicinal product in the paediatric population.
7.11	If we access cases that are not in the MAH database, is there an expectation that we will add the cases to the MAH database (if we determine they are the MAH's)?	MAHs should follow the established procedures when they receive information on a case that they are not aware of.
7.12	When selecting the active substance, can it be filtered by route of administration (e.g. topical, injection, oral, etc.)?	EVDAS filters are described in detailed in section 'MAH pharmacovigilance queries dashboard' slides 42-101 of the eLearning module: EVDAS training for Marketing Authorisation Holders (EV-M5b). There is no filter for the route of administration. Information on the route of administration can be found in the outputs: eRMR (slide 151), Line listing (slide 156) and ICSR form (slide 165), described in the EVDAS training for Marketing Authorisation Holders (EV-M5b).
7.13	Can we use the ad hoc reference period capability for our 6 month reviews instead of the fixed reference period?	Slide 84 of the eLearning module EVDAS training for Marketing Authorisation Holders (EV-M5b), states that the reference period of the ad hoc eRMR is restricted to 3 months and 2 weeks in the past from the day the report is run. The users are therefore able to define the reference period as being as short as a single day or as long as 105 days. In other words users cannot get an eRMR with a reference period of 6 months using the ad hoc eRMR, they need to use the fixed reference period.

Ref.	Question	Answer
7.14	In the context of credential to be used to retrieve outputs from EVDAS, once an eRMR is exported, is it necessary to be registered with EVDAS to retrieve line listings via the hyperlink?	Yes, it is necessary to be registered into EVDAS to obtain the line listings associated with the eRMRs.
7.15	In the context of credentials to be used to retrieve outputs from EVDAS, once a line listing is exported, is it necessary to be registered with EVDAS to retrieve ICSR via the hyperlink?	To retrieve the ICSR forms via the hyperlink in the case line listing, the EVDAS user can click on the hyperlink and access the individual case. To do so the EVDAS user also needs to enter the EVWEB credentials.

Signal management teams, where experts do not have a EVDAS scientific user profile, can access ICSRs directly from EVWEB, for which they need to be also registered. |
| 7.16 | What documentation do MAHs need to have/keep with regards to the signal detection and management activities when monitoring EudraVigilance? | MAH need to retain documentation related to the management of signals including signal detection activities using EudraVigilance data; this should be in line with the pharmacovigilance procedures described in the MAH's PSMF. |

Ref.	Question	Answer
7.17	When you download an eRMR, you can distribute to others who can see it for assessment but it seems they won't be able to click link to see line listing (i.e. would you need to go back to person with access to EVDAS?). When will we be able to test EVDAS platform and various process scenarios in the test environment?	In order the access data from EVDAS and retrieve line listings from the hyperlinks provided in the eRMR, the users must have credentials to use EVDAS. No EVDAS training environment will be available.
7.18	Question related to EVDAS: will there be any test or example system outputs prior to go-live (i.e. excel format eRMR) for configuring or testing systems for managing the data?	Outputs of EVDAS, eRMR's, Line listings and ICSR forms are fully described in the eLearning EVDAS training for Marketing Authorisation Holders (EV-M5b)
7.19	For generic drugs, do all the MAH should query EVDAS or only the MAH of the innovator drugs?	All MAHs without distinction shall monitor EudraVigilance data according to Commission Implementing Regulation (EU) No 520/2012.
7.20	Is it possible for a company to only use the statistical query in EVDAS and to stop to perform a statistical test in his own database?	MAHs should determine and decide the relevant processes and activities in order to comply with their pharmacovigilance obligations and the European legislation.

Ref.	Question	Answer
7.21	When will the list of HLSA registered in EVDAS available for all MAHs?	This will be made available on 22 November 2017.
7.22	Question about "ADRREPORTS.EU portal" we can find information on reports of suspected side effects (also known as suspected adverse drug reactions) for authorised medicines in the European Economic Area (EEA). What if my product (NAP) is not there? Why is it not there? Should I contact EMA helpdesk?	Please contact EMA helpdesk (https://servicedesk.ema.europa.eu).
7.23	Will it be based on the companies XEVMPD products including formulation or just active ingredient?	Access to EudraVigilance data for MAHs is provided at the level of the 'active substance high level'. Following the analysis of the data, MAHs should consider the relevant information for the safety of their products.
7.24	Is there a test area available we can log into and have a look around and familiarise with EVDAS?	No EVDAS training environment will be available. Users can access EVDAS on 22 November 2017

Ref.	Question	Answer
7.25	Can we run an eRMR on all active substance high levels or only the ones including an active substance for which we are MAH?	Access to EudraVigilance data in EVDAS for MAHs is provided at the level of the 'active substance high level'. EudraVigilance 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.

The eRMR and line listings are based on level 1 access according to the EudraVigilance Access Policy and the output-fields are the same regardless of the substance and regardless of the MAH querying the database.

When retrieving ICSR forms from the link provided in the case line listing, different levels of access (level 1, 2A and 3) as per the EudraVigilance Access Policy are provided depending on the MAHs and the medicinal products for which they hold a marketing authorisation in the EEA. |
| 7.26 | For a defined eRMR, for one High Level Active Substance, would it be possible de performs only the analysis on the indication/population/route of administration covered by the Marketing Authorisation of the concerned MAH? | The eRMR will provide the number of cases (during the reporting interval and in total) per route of administration (when reported) for the DECs. This will take into account the three most frequent routes of administrations as reported.

The eRMR will also provide the number of cases per drug-event combination when the route of administration has not been reported.

This will be irrelevant for substances with only one authorised route of administration but more relevant for substances with several routes of administrations.

This information should be put in the context of the number of cases during the period and cumulative |

Ref.	Question	Answer
7.27	Training Module EV- M5b Jan 2017: Is a MAH able to view data in the eRMR for the MAH's product(s) only, or can the MAH view the data for all MAHs for the selected active substance (MAH's product), if there is more than one MAH for this substance?	Access to EudraVigilance data in EVDAS for MAHs is provided at the level of the 'active substance high level'. EudraVigilance 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. The eRMR and line listings are based on level 1 access according to the EudraVigilance Access Policy and the output-fields are the same regardless of the substance and regardless of the MAH querying the database. When retrieving ICSR forms from the link provided in the case line listing, different levels of access (level 1, 2A and 3) as per the EudraVigilance Access Policy are provided depending on the MAHs and the medicinal products for which they hold a marketing authorisation in the EEA.
7.28	You informed us that EVDAS will be available from 22 November 2017. What will be the dates of the first fixed period e-RMR pre-generated by EMA? Will it be 01Jun2017-30 Nov2017?	EMA is currently evaluating different options; one option is to provide an eRMR on 22 November 2017 with a reference period from 1 May 2017 to 31 October 2017. Alternatively, an eRMR can be provided on 1 Dec 2017 covering the reference period from 1 June to 30 November 2017. These options will be confirmed in due course.

Ref.	Question	Answer
7.29	Training Module EV-M5b Jan 2017: "plenty of different routes". A priori: If a product with several routes of administration, the 3 most frequent are presented. Could you please confirm?	The eRMR will provide the number of cases (during the reporting interval and in total) per route of administration (when reported) for the DECs. This will take into account the three most frequent routes of administrations as reported. The eRMR will also provide the number of cases per drug-event combination when the route of administration has not been reported. This will be irrelevant for substances with only one authorised route of administration but more relevant for substances with several routes of administrations. This information should be put in the context of the number of cases during the period and cumulative. See as an example an extract from an eRMR:
7.30	Can we have eRMR with zero signals?	If the question is referring to Signals of Disproportionate Reporting (SDR), the answer is potentially yes. This may relate to medicinal products with a very low reporting rate of ADRs and for which the ADRs reported have been commonly reported for the rest of the substances in the EudraVigilance database.
7.31	How long will level 2B access be available for MAHs for a defined signal?	Level 2B is always available provided that the MAH users have been granted access by the EU QPPV and the user confirmed agreement with the confidentiality undertaken when requesting L2B access.
7.32	According to your experience, from the authorities' side, what is the mean time interval between e-RMR availability and signal validation?	The time to be dedicated for signal detection and assessment processes depends on many different variables including the substance and the number of cases received for the DECs selected for review.
7.33	Regarding EVDAS screening, should it be performed by specific PT or it can be done with the PT prompt free of PT's.?	The EDVAS dashboard allows performing queries using the MedDRA hierarchy. The prompt is not mandatory and therefore when it is not completed, the system will retrieve all the cases received in the EVPM for the selected active substance when it has been coded as suspect/interacting.

Ref.	Question	Answer
7.34	If it is not possible to search by dosage form or indication, how valuable can the results be for substances with totally different dosages and dosage forms (e.g. oral laxative vs injectable mineral supplement)?	Access to EudraVigilance data for MAHs is provided at the level of the 'active substance high level'. Following the analysis of the data, MAHs should consider the relevant information for the safety of their products.
7.35	For the line listing in EVDAS - is there a limit to the number of rows?	The current limit to display ICSR in the line listing is 100,000 cases. 2,738 cases can be exported in excel. 100,000 cases can be exported in csv.
7.36	When the EVDAS user manual will be published?	This will be published in October 2017
7.37	Have you planned to organize any webinar to explain EMA methodology on your signal assessment in order to allow the MAH to be more familiar and share your experience on this process	A DIA/EMA information day on Signal Management will take place at the EMA premises on 27th October 2017. See published Agenda: http://www.ema.europa.eu/docs/en_GB/document_library/Agenda/2017/02/WC500222156.pdf
7.38	When using the fixed-period, users can select an eRMR containing multiple active substances. Is there a limit to how many active substances can be grouped in a single eRMR?	There is no limit in the number of substances users can select in the prompt for the fixed eRMR, but the limit is in the output that is generated. This limit is 100,000 rows (= 100,000 drug-event combinations) and applies both to the eRMR report and the line listing. If the user selects substances that would generate an output larger than 100,000 rows, no results will be given and an error message will be displayed.

Ref.	Question	Answer
7.39	What is the proper way to handle closely monitoring topics in point of view of signal management (over including them in PSUR)?	The access to the EudraVigilance data by MAHs does not change the format of the PSURs. When analysing safety issues under close monitoring, MAHs should consider the cases held in EV as another source of information that may enhance the assessment of those issues. Topics requested by a regulator to be closely monitor should be reported in Section 15 of the PSURs as indicated in GVP Module VII.
7.40	Will we have also the device technical complaints coding reflected in the eRMR if associated to an AE?	The eRMR is an output from EV and contains the drug-event combinations as coded in the ICSRs. If cases related to medical devices are submitted to EV as ICSRs and coded with a suspect /interacting drug and suspected ADRs, the relevant drug-event combinations will appear in the eRMR.
7.41	Do the MAH have the obligation to do the same signal detection exercise concerning the technical complaints in EVDAS?	Medical devices have their specific legislations to be followed. If the complaint related to medical devices contains suspected ADRs, MAHs should follow the standard process for the signal management procedure.
7.42 **(new)**	e-RMR: is the ROR and the threshold number of cases always based on cumulative data?	The criteria for a Signal of Disproportionate Reporting (SDR), which include the ROR value, are based on the total number of spontaneous reports. The use of subgrouping by geographical region should be taken into account. An SDR is considered in the eRMR when there is an SDR in at least one of the regions. This means that the ROR should be greater than one in one region and the total number of spontaneous reports in the same region should be above 3 or 5, depending if the substance is included in the additional monitoring list or not.

Ref.	Question	Answer
7.43 **(new)**	EVDAS data access. What will be the level of data access in EVDAS? Will we have access to our own data only? Or in addition to publicly available data (e.g. literature cases)? Or to all cases (and at what detail level)?	Access to EudraVigilance data in EVDAS for MAHs is provided at the level of the 'active substance high level'. EudraVigilance 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. The eRMR and line listings are based on level 1 access according to the EudraVigilance Access Policy and the output-fields are the same regardless of the substance and regardless of the MAH querying the database. When retrieving ICSR forms from the link provided in the case line listing, different levels of access (level 1, 2A and 3) as per the EudraVigilance Access Policy are provided depending on the MAHs and the medicinal products for which they hold a marketing authorisation in the EEA.
7.44 **(new)**	EVDAS interface. Will EVDAS provide an interface to feed EVDAS data into other signal detection applications (e.g. Empirica Signals)?	Currently there is not functionality foreseen that permits exporting EVDAS data for further integration with other marketed applications or software designed for signal detection.
7.45 **(new)**	Proposal for a roadmap To make signal detection efficient it is the key to have a strong control dataset. Are there any plans to provide a merged reference database with information from several regulators/organizations (EMA, FDA, PMDA, WHO …)? How can MAH effectively identify duplicates across different databases?	MAHs can organise according to their medicinal product portfolio which data sets they wish to utilise for signal detection or overall safety monitoring to fulfil their pharmacovigilance obligations. In the EU, the requirements for MAHs as regards EudraVigilance are clearly defined in the pharmacovigilance legislation and GVP Module IX. ICH E2B has defined the concept of the world-wide unique identifier for ICSRs so they can be traced in various pharmacovigilance systems in order to avoid or reduce the risk of duplication.

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). If the ICH IG is updated then GZ will be implemented in EU as well.
8.2 **(updated)**	When can we expect sample files having attachments?	Example files have been created and published on the EMA website: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500230516
8.3	What will be the sequence of attachment embedding in the ICH E2B(R3) file? 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	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.
	
	`<xsl:if test="$XEVMPD=1"><xsl:choose>`
	
	`<xsl:when test="string-length(hl7:code/@displayName) > 0 and string-length(hl7:code/@code) > 0 and hl7:code/@codeSystem ='SUB-code'"><xsl:value-of select="hl7:code/@displayName"/></xsl:when>`
	
	`<xsl:otherwise> <xsl:value-of select="hl7:name"/></xsl:otherwise></xsl:choose></xsl:if> <xsl:if test="$XEVMPD!=1"> <xsl:value-of select="hl7:name"/></xsl:if> </xsl:if>`
		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.
		
		The setting can be applied in the BFC file "OIDs.xsl":
		
		`<!-- Use Recoded EudraVigilance product and substance names instead of verbatim term --><!-- set value to 1 to use EV recoding--><xsl:variable name="XEVMPD"></xsl:variable><!-- EV product -->`
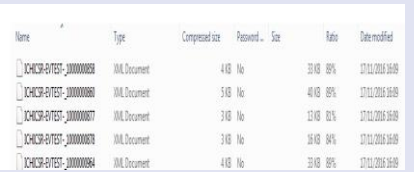
Ref.	Question	Answer
8.5	Will the recoding for suspect drug substance or product names performed by EMA in the EudraVigilance database assign the corresponding MAH in B.4.k.4.3 / G.k.3.3. if this information is available? Does the EMA filter allow to define downloads based on product level, thus, allows for searches for fixed dose combinations to only list ICSR which actually contain the combination product?	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.
8.6	There is a discrepancy between wording in GVP VI and the EU HL7 Implementation Guide concerning the use of local language- GVP VI allows for original language to be provided only where this is requested by either the concerned member state CA or by EMA. The EU HL7 Implementation Guide simply states that the MAH 'shall provide the original verbatim text'.	The EU IG has been revised and published; the text has been bought in line with the revised GVP VI.

Ref.	Question	Answer
8.7	In tests files loaded from EVWEB test module there is no batch number (N.1.2) available and the date of batch transmission (N.1.5) is masked by a nullflavor, so they had to be manually added into the files in order to be processed into database. Will it be the same in production environment?	The access policy does not give access to these fields of the original data, therefore they are currently not provided. This request is being reviewed and the generation of automated text to populate these fields is being planned to support the upload process by MAHs.
8.8	Is there a R3 field viewer? So that we can see R3 files in human readable format to manually process?	Yes, EVWEB allows organisations to up load E2B(R3) files into the application (workspace), from the application it is possible to generate human readable outputs.
8.9	Have gateway validation rules to determine ACK and NACK from cases being transmitted been finalised for EMA? -.that is for R3 format ICSRs	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.
8.10	Could you confirm "E2BR3/R2 XML Testing" is mandatory to obtain our activated access to production environment? Do we have to send you back R3 converted files in e2BR2 format?	If there is no significant change to the database, then it is not mandatory to perform testing with the EMA; however we strongly recommend that you perform some testing of your own in the XCOMP environment to ensure that you will still be able to transmit cases when the new system goes live.

Ref.	Question	Answer
8.11	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. If any modification has been done, testing with EMA is mandatory.
8.12	Once the implementation of the new R3 format of the safety database is done, MAH has to performance the testing with EMA. 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. This will be reviewed if testing requests increase.
8.13 **(updated)**	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.
8.14	What is the maximum allowed embedded file size?	As descried 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
8.15	Regarding the Download functionality. Considered the effect of the EMA re-coding 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? 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? 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) 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?	The EU implementation guide has been updated and includes further details on how drugs are classified against XEVMPD data. In accordance with the access policy L2 access will provide the verbatim text as received in EudraVigilance for the product and substance names. In addition, the as classified product/substance name will also be made available in a separate field. L2 access is given based on active substance(s).

Ref.	Question	Answer
8.16	Regarding the Download functionality.

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?

The reason why it is important to understand this data and the potential effects of the re-coding, most commercial safety databases will try to match the product name against a centrally stored repository within the safety system itself and often if there is no match, the product remains un-coded upon upload in the safety system, as a consequence

We would be forced to manually recode the product in this circumstance

No match of the product also means that information such as causality does not appear in the front end upon upload again forcing a manual intervention to review the xml message for this information | The EU implementation guide has been updated and includes further details on how drugs are classified against XEVMPD data.

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. |

Ref.	Question	Answer
8.17	Regarding the Download functionality. One other consideration for you, 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 screenshot below is what we saw in the pilot and yes this is not production, but as you can see the filename does not provide any meaningful information that an MAH can make use of? *(screenshot of file listing)*	The data of creation of the XML file will be included within the XML files themselves using the field N.1.5

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

Ref.	Question	Answer
9.1	We have not yet had any notification of testing dates from the EMA. Could you please let me know when to sign up for a testing slot?	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. Please refer to testing steps at the EudraVigilance: electronic reporting webpage and the EudraVigilance change management webpage.
9.2 **(updated)**	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	If we are EV Post users, is it mandatory to do the test in xCOMP? If it is necessary, should we book an slot?	Yes, EVPOST users must test before being allowed to use EVPOST in production. To perform testing a testing slot needs to be booked with EMA.

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? Will the usual roughly 10 scenarios be available?	Test ICSRs can already be downloaded from XCOMP, test files can be downloaded from the EudraVigilance pages on the EMA website.
9.6 **(updated)**	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. 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	For EVWEB user, I understand there is no need to book slot for testing. Is it correct?	That is correct.

Ref.	Question	Answer
9.8	Does the EMA backward/forward conversion tool require another tool to actually convert R3 to R2, correct? 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? 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. It would be unusual for organisations to validate XSLT processors as organisations would not validate programing compliers such as for using Java programs.
9.9	In the EudraVigilance: Electronic reporting states that Third party service providers should complete all the testing steps (1 through 6). If we are using EVWEB for transmission is that required? Or just testing in XCOMP without booking a timeslot is enough?	If you are only using EVWEB online forms for creating and sending ICSRs there is no need to perform testing. Only gateway organisations and EVPOST users need to perform the testing. It is recommended that EVWEB users follow the published eLearning courses and get familiar with XCOMP.

Ref.	Question	Answer
9.10	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 'EudraVigilance change management', section 'On the new EudraVigilance database, where can I find detailed information and guidance? (Updated July 2017)'. Please refer to the document 'EU reference instances' and 'EU E2B(R3) testing files'.

10. Go-Live Planning

Ref.	Question	Answer
10.1 **(updated)**	What are the plans and expectations for the actual changeover of the EudraVigilance database from the old structure to the new one?	The following EMA IT systems will be affected by the planned downtime period (from 8 November to 21 November 2017) for the launch of the new EudraVigilance system (Human) on 22 November 2017 (09:00 UK time): EudraVigilance Human, EudraVigilance Veterinary, EudraVigilance registration, EVDAS, EVVET data warehouse, Art.57/XEVMPD database, PSUR repository, eAF, EudraCT, EudraCT data warehouse. Please refer to the Technical Note (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/09/WC500235775.pdf) for further instructions to Member States, applicants, marketing authorisation holders and sponsors of clinical trials.
10.2	Is there a grace period for MAHs to be able to get started with monitoring activities in order to be compliant with requirements? E.g. start 6 months after final publication of GVP Module IX. Would this be inclusive of 6 months from receiving access to a functional eRMR so that we can work out our processes?	Please refer to dedicated communication from the Agency on its website: (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b).

Ref.	Question	Answer
10.3 **(updated)**	What is the date that a live, fully functioning eRMR inclusive of working hyperlinks, dummy data if real data isn't feasible will be available to us? - whilst the published training material helps until end-users can run this process end to end ,the business process cannot be fully finalized	EVDAS will be available to the users on 22 November 2017. Please refer to the eRMR template published on the EV training page: (http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500232321)
10.4	27 October is the target for EMA training being offered on signal detection. Are there plans for offering any earlier training sessions ahead of the November Go Live date? We wish to allow sufficient time for training and any adjustments that may need to occur to our process as a result of the training. What can be done to provide signal detection training earlier in this roll-out as a way to help mitigate any compliance risks with the November timing?	There are no plans for other training sessions dedicated to signal detection. MAHs should use the training materials provided and make use of the webinars and info days programmed.

Ref.	Question	Answer
10.5	If the MAH has sent an initial report to the NCA before 22nd November 2017, can any subsequent follow-ups be sent to EudraVigilance after 22nd November 2017?	Yes, the EudraVigilance system will allow MAH to follow-up (after 22 Nov 2017) on ICSRs previously sent to NCAs (before 22 Nov 2017).
10.6	In case of nullification, do we need to make sure that a report previously submitted to Local NCA, is sent for nullification to EudraVigilance after 22 Nov2016?	Yes, nullification of ICSRs, previously submitted to NCAs, should be sent to the EudraVigilance system as of 22 Nov. 2017.
10.7 **(new)**	Do we need to screen the authority webpages (exp. Bfarm) after 22-Nov-2017 as well? Or can we start screening via EudraVigilance immediately? Will there be an interim period?	As of 22 November 2017, the simplified reporting rules set out in the pharmacovigilance legislation will apply.

This means that as of 22 November 2017 you will obtain access to all reports of suspected adverse reactions that occurred in the EEA via EudraVigilance.

However, it is recommended to perform in the immediate launch of the new system a reconciliation between the authority webpages (exp. Bfarm) and the data retrieved from the EV system to assure that no ICSR has been missed during the transition period.

Please refer to the EudraVigilance go-live plan, which provides further details also in respect of the transitional arrangements during the cutover period from the current to the new EudraVigilance system.

This cutover period will be initiated on 8 November 2017 and will end on 21 November 2017.

Please refer to the EudraVigilance Change Management webpage, where there is a dedicated section on the go-live planning:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000165.jsp |

Ref.	Question	Answer
10.8 **(new)**	Special submission scenarios. Is there a centralized business continuity requirement at EMA only, or is it expected that MAHs have to send cases to the NCAs in a business continuity situation?	The EU Regulatory Network has prepared the EudraVigilance go-live plan, which describes the stakeholders impacted and sets out the technical and business process related aspects as well as alternative arrangements for reporting of ICSRs that need to be planned for by stakeholders to ensure a successful transition from the current to the new EudraVigilance system in November 2017. Procedures are in place for urgent reporting of important safety information and are reiterated in this go-live plan. The EudraVigilance go-live plan is to be published in the 1st week of October 2017. The routine process of the steps to follow in case of a system failure at the sender or receiver side is described in the EU ICSR Implementation Guide. Please refer to: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/04/WC500165979.pdf

Ref.	Question	Answer
10.9 **(new)**	How should MAHs report ICSRs to EudraVigilance in order to stay compliant during the scheduled EudraVigilance downtime prior to implementation of the new EudraVigilance system? Will E2B submission to NCAs continue during this time frame in accordance to the interims reporting requirements for ICSRs? How are the cutover modalities arranged? We understand there will be a significant downtime at EMA. In which format will EMA expect cases during the downtime (any CDs during the outage, for example?), and how will the potential impact on compliance be addressed?	The EU Regulatory Network has prepared the EudraVigilance go-live plan, which describes the stakeholders impacted and sets out the technical and business process related aspects as well as alternative arrangements for reporting of ICSRs that need to be planned for by stakeholders to ensure a successful transition from the current to the new EudraVigilance system in November 2017. Procedures are in place for urgent reporting of important safety information and are reiterated in this go-live plan. The EudraVigilance go-live plan is to be published in the 1st week of October 2017.

Ref.	Question	Answer
10.10 **(new)**	EudraVigilance go-live planning. Please can the transition plans for 22-November be clarified, especially the reporting requirements to local NCAs? - When will the transition period start? - Will the EudraVigilance Gateway be available during the transition period to submit ICSRs to NCAs? - Will MAHs be required to report to NCAs using an alternative process (e.g. paper/fax) during the EudraVigilance downtime? - How should we treat cases that have been submitted immediately before the start of the transition period, but have not received acknowledgements? Should they be resubmitted on 22-November 2017?	As of 22 November 2017, the simplified reporting rules set out in the pharmacovigilance legislation will apply. This means that as of 22 November 2017 MAHs will obtain access to all reports of suspected adverse reactions that occurred in the EEA via EudraVigilance. Please refer to the EudraVigilance go-live plan, which provides further details also in respect of the transitional arrangements during the cutover period from the current to the new EudraVigilance system. This cutover period will be initiated on 8 November 2017 and will end on 21 November 2017. Please refer to the EudraVigilance Change Management webpage, where there is a dedicated section on the go-live planning: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000165.jsp The EudraVigilance go-live plan is published on EMA website (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/09/WC500235774.pdf).

Ref.	Question	Answer
10.11 **(new)**	Regarding the planned EV downtime. If we receive a negative ACK for a submission sent to a NCA prior to the downtime, will we be required to correct and resubmit when the Gateway is back up?	Yes
10.12 **(new)**	Regarding simplified reporting. What should be the date used to identify non-serious reports requiring submission to EV? Any case with a Day 0 on or after 22 November?	Yes. Please refer also to the EudraVigilance go-live plan, published on EMA website (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/09/WC500235774.pdf) which will include further instructions and guidance as regards non-serious reports which cannot be reported to NCAs (where required) during the cutover period of 8 to 21 November 2017.
10.13 **(new)**	Regarding simplified reporting . Should MAHs continue to report Liechtenstein domestic cases to the NCA, Swissmedic and EV after 22 November, or should these be submitted only to EV?	Liechtenstein is part of the EEA and therefore the simplified reporting rules apply accordingly. As regards the reporting to Swissmedic, the reporting rules do not change. For details please liaise directly with Swissmedic.

Ref.	Question	Answer
10.14 **(new)**	Cases received within the safety department that have a company receipt date of prior to 22nd November. If they are reportable in Europe should they be sent to the relevant individual National Competent Authorities or to EMA? For example if the COI is UK should we sent to EMA or MHRA?	As of 22 November 2017, the simplified reporting rules set out in the pharmacovigilance legislation will apply. This means that as of 22 November 2017 you will obtain access to all reports of suspected adverse reactions that occurred in the EEA via EudraVigilance. Please refer to the EudraVigilance go-live plan, which provides further details also in respect of the transitional arrangements during the cutover period from the current to the new EudraVigilance system. This cutover period will be initiated on 8 November 2017 and will end on 21 November 2017. Please refer to the EudraVigilance Change Management webpage, where there is a dedicated section on the go-live planning: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000165.jsp The EudraVigilance go-live plan is published on EMA website (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/09/WC500235774.pdf).

11. Others

Ref.	Question	Answer
11.1	When will you publish the update Q&A integrating the Q&A of previous sessions?	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?	The knowledge evaluation is intended for new non-commercial sponsors registering their organisation for the first time. There is no requirement for existing registered organisations using EVWEB to undertake the face-to-face training. Existing users of the system should follow the e-learning courses and do not need to take a competency assessment 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.
11.3 **(new)**	Can EMA provide an update on the latest information for "Brexit"?	Please refer to the EMA dedicated communications.

Ref.	Question	Answer
11.4 **(new)**	Can EMA provide an update on where IDMP stands and the plan/timeframe for use/implementation?	The legacy EV data have been migrated from the current ICH E2B(R2) format in compliance with the Art.57/xEVMPD database. Art.57/xEVMPD database contains the core data elements as defined in the ISO IDMP standard. 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. The legacy data from Article 57 will be migrated to the ISO IDMP format as detailed in the following EMA webpage on 'Implementation of the ISO IDMP standards' tp://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000645.jsp&mid=WC0b01ac058078fbe2