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Monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency

Questions and Answers

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This Questions and Answers (Q&A) document addresses a first set of frequently asked questions from marketing authorisation holders in preparation of the implementation of the monitoring of medical literature and entry of adverse reaction reports into EudraVigilance by the Agency in line with Article 27 of Regulation (EC) 726/2014.

This Q&A document will be regularly updated based on further questions received. All questions and answers are subject to evaluation and agreement by the pharmacovigilance governance.

Updates will be published at the [dedicated MLM webpage](#) of the Agency.

*Revision 2 includes a revised question 001 &, minor grammatical changes to some answers, replacement of question 006 with question 045 and addition of questions 46 - 48



Reference- ID	Question	Answer
001	<p>What is day zero for the marketing authorisation holder?</p> <p>The day when the article is available on the EudraVigilance website or when the European Medicines Agency (EMA) found the article in the dedicated literature reference databases?</p>	<p>The clock start for the reporting of a valid ICSR (day zero) is defined in GVP Module VI, chapter VI.B.7. <i>Reporting of Individual case safety reports (ICSRs)</i>. More specifically it is stated that "For ICSRs described in the scientific and medical literature (see VI.B.1.1.2.), the clock starts (day zero) with awareness of a publication containing the minimum information for reporting. Where contractual arrangements are made with a person/organisation to perform literature searches and/or report valid ICSRs, detailed agreements should exist to ensure that the marketing authorisation holder can comply with the reporting obligations".</p> <p>Furthermore, GVP Module VI, chapter VI.App2.7. "Day zero" indicates that "<i>although with weekly literature searching, day zero for a reportable adverse reaction present in an abstract is taken to be the date on which the search was conducted. For articles that have been ordered as a result of literature search results, day zero is the date when the minimum information for an ICSR to be valid is available</i>".</p> <p>For ICSRs described in the scientific and medical literature monitored by the Agency in accordance with Article 27 of Regulation (EC) 726/2004, 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 marketing authorisation holders at the time of the publication of the outcome of the literature screening result "MLM Search Results" on the dedicated area of the EudraVigilance website. For records of potential ICSRs, the day zero is the date when the minimum information for an ICSR to be valid is available.</p> <p>For ICSRs described in the scientific and medical literature monitored by the Agency in accordance with Article 27 of Regulation (EC) 726/2004, 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</p>

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		<p>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. For records of potential ICSRs, the day zero for the MLM service is the date when the minimum information for an ICSR to be valid is available.</p> <p>For further details please refer to the Detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency (Doc. Ref. EMA/161530/2014).</p>
002	When will the full production start and which medicinal products are included in the service?	<p>The start of the full operation of the MLM service will take place on 1 September 2015 and will cover the top 300 active chemical substance groups and 100 herbal groups. The top 300 active chemical substance groups can be identified using the list "Medical literature monitoring: substance and herbal substance groups" as published at the dedicated MLM webpage.</p>
003	Will marketing authorisation holders still need to do literature screening for brand names for the substance groups included in the Medical Literature Monitoring (MLM) service?	<p>The search strategy for each substance group included in the MLM service provided by the Agency will include brand names based on the following principle (see Detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency: Doc. Ref. EMA/161530/2014):</p> <p>"Substance Groups [INN name] or [Synonym] – A key string is defined for each substance group and is constituted of multiple components. The first component will be the INN name. The other components will be alternative names (variants) for the substances based on the Extended EudraVigilance Medicinal Product Dictionary (xEVMPD) or other reference sources".</p> <p>Alternative names (variants) will include medicinal product names (brand names) based on the information submitted by marketing authorisation holders in accordance with Article 57(2), second subparagraph of Regulation (EC) 726/2004 as well as variants for medicinal product names that have been reported in ICSRs to EudraVigilance.</p> <p>The search strategies will be published at the dedicated MLM webpage.</p>

Reference- ID	Question	Answer
004	If an individual case resulting from the MLM service of the Agency and created in EudraVigilance already exists in the marketing authorisation holder's safety database - does the marketing authorisation holder need to provide the EMA case number as follow-up information?	<p>In GVP Module VI, chapter VI.C.6.2.2.7. "Follow-up information" it is stated that <i>"marketing authorisation holders should also report follow-up information, where new administrative information is available, that could impact on the case management; for example, if new case identifiers have become known to the sender, which may have been used in previous transmissions (data element 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.1.11)). This information may be specifically relevant to manage potential duplicates"</i>.</p> <p>The marketing authorisation holder should therefore report the EMA world-wide unique case identifier as follow-up information for the individual case already existing in the marketing authorisation holder's database to the receivers where the individual case was previously reported by the marketing authorisation holder.</p>
005	For individual cases resulting from the MLM service of the Agency and downloaded by the marketing authorisation holder from EudraVigilance and imported to the company's safety database - can the marketing authorisation holder change the literature reports as per their own SOPs?	<p>The marketing authorisation holder can process the ICSRs originating from the new service in their safety database according to their own SOPs. The provisions set out in GVP Module VI and related guidance should be followed accordingly.</p> <p>More specifically, GVP Module VI, chapter VI.C.6.2.2.4. "Case narrative, causality assessment and comments" states the following:</p> <p><i>"Where available, comments from the primary source on the diagnosis, causality assessment or other relevant issue, should be provided in the data element 'Reporter's comments' (ICH-E2B(R2) B.5.2). Competent authorities in Member States and marketing authorisation holders may provide an assessment of the case and describe a disagreement with, and/or alternatives to the diagnoses given by the primary source (see VI.C.6.2.2.3.). This should be done in the data element 'Sender's comments' (ICH-E2B(R2) B.5.4), where discrepancies or confusions in the information notified by the primary source may also be highlighted. Where applicable, a summary of the points of concerns and actions proposed should also be included in the data element 'Sender's comments' (ICH-E2B(R2) B.5.4), if the ICSR leads to notification of an emerging safety issue (see VI.C.2.2.6.). The degree of suspected relatedness of each medicinal product to the adverse reaction(s) may be indicated in the data element 'Relatedness of drug to reaction(s)/event(s)' (ICH-E2B(R2) B.4.k.18), which should be</i></p>

Reference- ID	Question	Answer
		<p>repeated as necessary. This also allows presenting the degree of relatedness from different sources or with different methods of assessment".</p> <p>For guidance on "downgrading" of individual cases refer to GVP Module VI, chapters VI.B.2. "Validation of reports" and VI.C.6.2.2.7. "Follow-up information".</p>
006	<p>Following the publication of the detailed guide for the MLM service, I have a question regarding the inclusion and exclusion criteria for processing of ICSRs. I note in the seriousness section of that particular document that non-serious case reports that occur outside of the European Economic Area (EEA) are excluded from the process. Is this correct?</p> <p>Does this mean that non-serious ICSRs that occur outside of the EEA will not be made available to marketing authorisation holders?</p> <p>If this is so, should marketing authorisation holders be screening for these types of reports in parallel for Periodic Safety Update Reports (PSURs) and/or signal detection purposes?</p>	<p>The reporting modalities regarding suspected non-serious adverse reactions are described in GVP module VI, chapter VI.C.4 "Reporting modalities".</p> <p>Based on these reporting modalities, only individual cases of suspected non-serious adverse reactions that occur within the EEA are included in the service provided by the Agency in accordance with Article 27 of Regulation (EC) 726/2004.</p> <p>Marketing authorisation holders need to continue to screen the scientific and medical literature to fulfil their other pharmacovigilance obligations e.g. in the context of preparing Periodic Safety Update Reports (PSURs) or Risk Management Plans (RMPs) as applicable.</p> <p>Marketing authorisation holders also have an obligation to screen the scientific and medical literature as a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues.</p> <p><i>This question has been removed since it is no longer applicable. Please see question 045 for non-EEA non-serious cases</i></p>

Reference- ID	Question	Answer
007	<p>I could not identify in the legislation or in the detailed guide whether marketing authorisation holders still have to look in other databases (different from those that are going to be screened by the MLM service) for the substance groups covered by the Agency?</p> <p>Do marketing authorisation holders need to perform literature search beyond what is provided by the literature reference databases covered by the Agency's MLM service?</p>	<p>Directive 2001/83/EC, paragraph 107(3) indent 3, states the following: <i>"For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004, marketing authorisation holders shall not be required to report to the EudraVigilance database the suspected adverse reactions recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions"</i>. The requirements are further defined in GVP Module VI, chapter VI.B.1.1.2. "Literature reports" are further specified following: <i>"The marketing authorisation holder should ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the medicinal product properties"</i>⁵. <u>In addition, marketing authorisation holders should have procedures in place to monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorisation, and to bring them to the attention of the company safety department as appropriate</u>". For further information on what literature should be screened, refer also to GVP Module VI, chapter VI. Appendix 2 "Detailed guidance on the monitoring of scientific literature" and chapter VI .App2.2. "Where to look". In summary, marketing authorisation holders need to continue to monitor all other medical literature not covered by the literature reference databases applied for the service by the Agency in accordance with Article 27 of Regulation (EC) 726/2004. This includes scientific and medical publications in local journals in countries where medicinal products have a marketing authorisation. For very specialised medical fields, for certain types of medicinal products or where safety concerns are subject to non-clinical research, marketing authorisation holders should establish the most relevant source of published literature for each product (see GVP Module VI, chapter VI.App2.2. "Where to look").The reporting obligations of suspected adverse reactions by marketing authorisation holders for the scientific and medical publications not covered by the Agency remain as outlined in GVP Module VI. Nevertheless, marketing authorisation holders need to continue to screen the scientific and medical literature to fulfil their other pharmacovigilance obligations e.g. in the context of preparing Periodic Safety Update Reports (PSURs) or Risk Management Plans (RMPs) as applicable. Marketing authorisation holders also have an obligation to screen the scientific and medical literature as a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues.</p>

Reference- ID	Question	Answer
008	Are marketing authorisation holders required to download the cases from EudraVigilance and import to their safety database or is it sufficient to prevent re-submission of duplicates?	Whilst there is no obligation for marketing authorisation holders to download ICSRs from EudraVigilance that result from the service provided by the Agency and import the reports in the local safety database, marketing authorisation holders need to align their literature review and adverse reaction reporting processes to comply with their legal obligations as regards to the operation of a pharmacovigilance system and recording, reporting and assessment of pharmacovigilance data as outlined in TITLE IX of Directive 2001/83/EC and Regulation (EC) 726/2004, as well as the Commission Implementing Regulation (EU) 520/2012 and national legislation as applicable.
009	Do we need to have exactly the same data of an ICSR or is it sufficient to be able to cross-reference with the EudraVigilance database?	<p>The marketing authorisation holder can process the adverse reaction reports originating from the Agency's medical literature monitoring service in their safety database and provide for example an assessment of the case, describe a disagreement with, and/or alternatives to the diagnoses given by the primary source and/or indicate the degree of suspected relatedness of each medicinal product to the adverse reaction(s).</p> <p>The information related to an ICSR in a company's safety database therefore may not necessarily mirror exactly the same information as held in EudraVigilance.</p> <p>Reconciliation of the individual cases should be facilitated by cross-reference to the worldwide unique case safety identifier (ICH E2B (R2) A.1.10.2).</p> <p>The way how the "cross-referenced" reports are being processed including the handling of follow-up information or case nullification should be defined in the company's SOPs.</p>
010	For which period are search results and review results available?	<p>The search results with the literature records originating from the search are published at the dedicated area of the EudraVigilance website under "MLM Search Results" at the next calendar day. The "MLM Search Results" are published by 9 a.m. UK GMT.</p> <p>The screening results with the outcome of the screening of each literature record are also published by 9 a.m. UK GMT at the next calendar day (following the completion of the screening) at the dedicated area of the EudraVigilance website under "MLM Search Results".</p>

Reference- ID	Question	Answer
		<p>A literature record referenced in the "MLM Search Results" list is moved to the archive at the next calendar day following publication of the screening result for this record.</p> <p>All historic "MLM Search Results" records can be accessed in the "Archive" of the Medical Literature Monitoring section of the EudraVigilance restricted area, where the files are chronologically saved and sorted by month and year. The file name includes the date based on the following format YYYY/MM/DD.</p> <p>For further reference see chapter 4.3. "Archive" of the user manual (Doc. Ref. EMA/274835/2015).</p> <p>Note: calendar days are defined in the Detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency Doc. Ref. EMA/161530/2014)</p>
011	Will there be one Excel (.xlsx) file per calendar day or is this a cumulative list?	<p>For the "MLM Search Results", the Excel file reflects first the search results listing each identified literature record and subsequently the outcome of the screening result for each record (see also answer to question 013).</p> <p>The "MLM ICSRs" list is cumulative in the sense that each literature record including the outcome of the screening results is maintained in this list until the processing of potential or confirmed ICSRs and the follow-up, where applicable, are completed.</p> <p>Thereafter, each literature record is moved to the archive. Records of the "MLM ICSRs" files are chronologically saved and sorted by month and year in the archive.</p> <p>In addition to the daily lists, monthly cumulative lists for the "MLM Search Results" and "MLM ICSRs" are published early the following month, e.g. the November cumulative list was published in the first week of December.</p>
012	The service will start on the 1st September 2015. What will be the concerned marketing	As of 1 st September 2015 the service provided by the Agency is fully operational in accordance with Article 27 of Regulation (EC) 726/2004.

Reference- ID	Question	Answer
	authorisation holders' commitments?	<p>It is important that concerned marketing authorisation holders follow the instructions provided at the MLM webpage "How should concerned marketing authorisation holders prepare for the new service?" and to adapt their business processes as necessary i.e.:</p> <ul style="list-style-type: none"> Concerned marketing-authorisation holders should not re-submit the ICSRs resulting from the medical literature monitoring service to EudraVigilance. <p><i>Unless otherwise specified by national legislation and guidance, concerned marketing authorisation holders should not submit the ICSRs resulting from the medical literature monitoring service to the concerned national competent authorities in the EEA.</i></p>
013	If a marketing authorisation holder identifies a literature case not available in EudraVigilance, what process should be followed by the marketing authorisation holder?	<ol style="list-style-type: none"> For the literature and the active substances subject to the service of the Agency pursuant to Article 27 of Regulation (EC) No 726/2004: <ul style="list-style-type: none"> If a marketing authorisation holder identifies one or more individual cases of suspected adverse reaction(s) and the individual case(s) for these adverse reaction(s) were not processed by the Agency, the marketing authorisation holder should notify the service desk immediately. The Agency will review and process the relevant ICSRs as applicable. For the active substances subject to the service of the Agency pursuant to Article 27 of Regulation (EC) No 726/2004 but when the literature is not included in the list of publications monitored by the Agency: <ul style="list-style-type: none"> If a marketing authorisation holder identifies one or more individual cases of suspected adverse reaction(s), the marketing authorisation holder should report the suspected adverse reaction(s) in line with the reporting modalities defined in GVP Module VI, chapter VI.C.4. "Reporting modalities".
014	If, after the 1st September, for a medicinal product covered by the EMA, a marketing authorisation	For individual cases of suspected adverse reactions from the literature and the active substances that are subject to the service of the Agency and which were reported by marketing authorisation holders to the Agency and/or the National Competent Authorities in the EEA before the 1 st September 2015,

Reference- ID	Question	Answer
	holder receives a follow-up for a literature case identified and submitted to EMA before the 1 st September 2015, should the marketing authorisation holder submit the new information to the EMA or not?	the marketing authorisation holder should submit the follow-up information to the previous receivers of the ICSRs as applicable (see Module VI, chapter VI.C.4. "Reporting modalities").
015	At which time will the ICSRs be available for download by the marketing authorisation holder each business day?	<p>In the MLM EVWEB area, the ICSRs can be accessed immediately as soon as the individual cases have been entered in EudraVigilance.</p> <p>In the EudraVigilance ICH ICSR Export Manager, the ICSRs can be downloaded at the next calendar day from 9.00 a.m. UK time (GMT/BST as applicable) following the day of the entry of individual cases in EudraVigilance.</p> <p>Note: calendar days are defined in the Detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency Doc. Ref. EMA/161530/2014)</p>
016	What will be the nomenclature for the EMA case ID?	The nomenclature is as follows: <2 letter country code>-MLMSERVICE-<sequential number>.
017	Can you provide guidance regarding the creation of a multiple case versus a single case? If the article reports the same adverse reaction without any details for 200 patients and the only patient information available is the gender, will the	<p>This will need to be assessed on a case by case based on the information provided in the literature record.</p> <p>As a general principle, the following applies:</p> <ul style="list-style-type: none"> i. If the literature record refers to a spontaneous report (unsolicited communication, which does not derive from a study or any organised data collection systems where adverse event reporting is actively sought) the literature can be excluded if <ul style="list-style-type: none"> • the data source refers to literature ICSRs, which are based on an analysis from a competent

Reference- ID	Question	Answer
	EMA create 200 single cases or one multiple case?	<p>authority database within the EU;</p> <ul style="list-style-type: none"> it presents data analyses from publicly available databases (including Vigibase) which describe adverse reactions, which occur in a group of patients with a designated medicinal product with the aim of identifying or quantifying a safety hazard related to a medicinal product; <p>ii. If the literature record is not a spontaneous report i.e. refers to a solicited report, the literature can be excluded if</p> <ul style="list-style-type: none"> it refers to an interventional study; it refers to aggregated data on patients.
018	What is the sender identifier and the message receiver identifier in the XML files resulting from the Agency's service?	<p>The ICSR Message Sender Identifier (ICH E2B R(2) A.1.3) is:</p> <ul style="list-style-type: none"> Empty, if the ICSR is downloaded from EVWEB; "MLMSERVICE" for the ICSR downloaded from the EudraVigilance ICH ICSR Export Manager. <p>The Message Receiver Identifier (ICH E2B R(2) A.1.4) is:</p> <ul style="list-style-type: none"> Empty, if the ICSR is downloaded from EVWEB; The identifier of the marketing authorisation holder logged on at the restricted area of the EudraVigilance website for the EudraVigilance ICH ICSR Export Manager.
019	Is it possible to forward the individual cases resulting from the MLM service of the Agency to the marketing authorisation holder so that we can upload the case in our safety database via the gateway connected to the Agency?	<p>The automatic re-transmission of ICSRs resulting from the MLM service of the Agency to the concerned marketing authorisation holders via the established gateway connections is technically currently not possible.</p>

Reference- ID	Question	Answer
020	If the marketing authorisation holder uploads individual cases that result from the Agency's MLM service, most probably the local safety database will generate an acknowledgement message (ACKs). Are these ACKs accepted by the EudraVigilance Gateway?	For ICSRs resulting from the MLM service of the Agency and downloaded from the MLM EVWEB area or the EudraVigilance ICH ICSR Export Manager, the marketing authorisation holder should disable the sending of ACKs to the EudraVigilance Gateway.
021	What is the impact on statistical signal detection; are marketing authorisation holders consequently asked to setup for statistical signal detection based on individual cases resulting from the Agency's service?	<p>The obligations of marketing authorisation holders as regards recording, reporting and assessment of pharmacovigilance data are outlined in TITLE IX of Directive 2001/83/EC, Regulation (EC) 726/2004 in TITLE II, Chapter 3 "Pharmacovigilance", the Commission Implementing Regulation (EU) 520/2012, Article 21</p> <p>"Signal management process" as well as national legislation as applicable. These obligations include also the need to setup for statistical signal detection based on ICRSs resulting also from the Agency's service as outlined in Article 27 of Regulation (EC) 726/2004.</p>
022	In the 'Inclusion and exclusion criteria for processing of Individual Case Safety Reports' (EMA/119265/2015) workflow chart presented within section 2.5 'One or more suspected adverse reaction(s)' pertaining to 'special situations'. The interpretation to the workflow chart I make reference to is that if the ICSR does not contain a suspected ADR	<p>As part of the entire screening process the aim is to record any missing information in relation to the following characteristics:</p> <ul style="list-style-type: none"> • Report Type • Identifiable Patient • One or more suspected substance/medicinal product • One or more suspected adverse reaction • Causality • Seriousness

Reference- ID	Question	Answer
	<p>that the case is entered without the ADR as the workflow reads 'Record missing adverse reaction information and progress with Step 6'.</p> <p>However the guidance (example text page 15 section 5.5.2) states that if the literature record refers to a special situation with no ADR then there is no case and this is excluded. Please can you clarify as to whether there is an inconsistency between the guidance notes and the process workflow or confirm how this information should be interpreted correctly.</p>	<p>As outlined in the introduction chapter of the Inclusion and exclusion criteria for processing of Individual Case Safety Reports (Doc. Ref. EMA/119265/2015) document, missing information will be handled in line with chapter 3.3, "Follow-up of individual cases" of the detailed guide.</p> <p>Confirmed ICSRs will be processed in line with the detailed guide.</p> <p>Note: If no identifiable reporter can be determined based on any of the steps outlined in chapter 2.2. "Identifiable Reporter", the literature record is moved to the exclusion group as follow-up will not be possible if the reporter cannot be determined.</p>
023	Are marketing authorisation holders asked to make the EMA aware of detected duplicate reports?	<p>There is no expectation of marketing authorisation holders to notify the Agency about duplicates detected in the company's safety database. Nevertheless, the process as described for question 006 should be followed.</p> <p>The Agency has published a process description for managing duplicates in the context of Medical Literature Monitoring (MLM) service on the Agency's dedicated MLM webpage.</p>
024	As regards the ICSR Export Manager: how can we get access to EV production environment?	<p>Every user registered with EudraVigilance will have access to the ICSRs resulting from the MLM service of the Agency through the MLM EVWEB area and the EudraVigilance ICSR Export Manager. The production environment was deployed on 15 June 2015.</p>

Reference- ID	Question	Answer
	Is this access per user?	
025	Reference is made to case processing following a transfer of a marketing authorisation. Our organisation became marketing authorisation holder following the transfer in December 2013. As part of our weekly literature search, we identified a case report (literature record publication date in 2015) with the date of occurrence of the suspected adverse reaction in January 2012 i.e. prior to the transfer of the marketing authorisation. As per our current practice, we do not process individual cases occurring prior to the transfer for expediting reporting (we consider these as legacy cases) but do consider them as part of our PSUR/signal management activities. Is this the correct practice?	<p>Taking into account that the company became marketing authorisation holder in December 2013 and the individual case was published in literature in 2015, the individual case should still be reported in line with the provisions set out in GVP module VI even if the date of occurrence was before the transfer of the marketing authorisation.</p> <p>GVP Module VI, chapter VI.App2.7. "Day zero" indicates that "<i>...although with weekly literature searching, day zero for a reportable adverse reaction present in an abstract is taken to be the date on which the search was conducted. For articles that have been ordered as a result of literature search results, day zero is the date when the minimum information for an ICSR to be valid is available</i>".</p> <p>The ICH E2B(R2) ICSR, section A.1.11 "Other case identifiers in previous transmissions" should be completed at least with the source(s) of the case identifier (e.g., name of the company, name of regulatory agency) (ICH E2B(R2) A.1.11.1) and where available other case identifier(s) previously assigned to the case (ICH E2B(R2) A.1.11.2).</p> <p>It is correct that the case should be taken into account as part of the PSUR/signal management activities.</p>

Reference- ID	Question	Answer
026	How could we conclude that the articles from the Excel of "MLM Search Results" or "MLM ICSRs" are version 0 (initial) or 1.0 (follow up)? Is there a specific column that indicates the version of the case report?	In the "MLM ICSR" the initial ICSR and the follow-up (FU) ICSR will appear in a separate row of the Excel file with a reference to the applicable literature record. The initial version of an ICSR will have columns X, Y and Z (FU creation date, FU transmission date (EV) and FU transmission date (NCA)) blank, whereas a follow-up version will always have the FU creation date (column X) and the FU Transmission date (EV) (column Y) populated. Column Z (FU transmission date (NCA)) will also be populated if applicable.
027	For individual cases that were found as duplicate in our (company A) safety database (MLM literature case was determined to be a duplicate of company A's individual case) - Would EMA like to receive a follow- up case with the MLMSERVICE world-wide unique identifier (for the example where the initial individual case was not received from MLMSERVICE and was submitted by company A to EMA before)?	Where a company identifies a MLMSERVICE literature case to be a duplicate of a company's individual case, which was previously submitted to EudraVigilance, there is a need to send a follow-up with the MLMSERVICE world-wide unique case identifier to EudraVigilance. See also question number 006.
028	After a marketing authorisation holder has screened the articles and decided which individual cases need to be downloaded, can we also filter according to the	Filtering of ICSRs based on the world-wide unique case identifier can be done using the MLM EVWEB area from where the corresponding ICSRs can be downloaded by the marketing authorisation holder.

Reference- ID	Question	Answer
	<p>world-wide unique case identifier using the EudraVigilance ICSR Export Manager? We would like to download each XML separately according to our screening.</p>	
029	<p>As per the 'Detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency, it states that "prior to the ICSR creation, a duplicate check is performed in EudraVigilance. This duplicate check focuses primarily on identifying ICSRs that might originate from the same article. Where one or more duplicates are identified, the world-wide unique case identifier is recorded (in the ICSR "Other case identifiers in previous transmissions")."</p> <p>This would seem to imply that if MLM identify follow-up for a case already reported into EudraVigilance, the 'new' MLM case will be retained as the</p>	<p>The duplicate management process applied in EudraVigilance is defined in the Guideline on detection and management of duplicate individual cases and Individual Case Safety Reports (ICSRs) (Doc. Ref. EMA/13432/2009). It is further detailed for the MLM service in line with a dedicated duplicate management paper published on the MLM webpage.</p> <p>The EMA's duplicate management process has always been to retain the two, or more, underlying duplicates as valid individual cases for the purposes of follow-up from the senders and to create a master case based on the underlying information. The master case is used for all pharmacovigilance purposes in EudraVigilance.</p> <p>More specifically, should one or more individual (duplicative) cases be identified during the MLM process as outlined in chapter 3.1 "Processing of confirmed ICSRs" of the detailed guide, the following steps are followed:</p> <ul style="list-style-type: none"> • If an individual case from only one sender organisation referring to the same literature record is identified in EudraVigilance, then this individual case serves as the basis for the creation of the MLMSERVICE individual case. The original world-wide unique case identifier (WWID) and receive date for this case will be retained. The receipt date will be the date the literature record was retrieved with the four minimum reporting criteria available and the sender's unique (case) safety report identifier (ICH E2B(R2) A.1.0.1) will be created as an MLMSERVICE number. This individual case will then be made available for download by concerned marketing authorisation holders. <p>Because case clustering in EudraVigilance is based on a combination of a message sender organization and the WWID, a master case will still need to be created for pharmacovigilance</p>

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	<p>master case file and the original safety report will be referenced as an E2B Report Duplicate within E2B tag A.1.11.2.</p> <p>If this is the correct interpretation of the Guidance, this contravenes ICH E2B R2, which states that no case should ever have more than one E2B Company Number or E2B Authority Number. Once designated this number should remain unchanged for any transmissions subsequent to the original transmission. When a sender has not previously received a valid E2B/M2 report electronically, the identifiers (content and format) in A.1.0.1 and A.1.10.1 or A.1.10.2 should be identical. However, as stated re-transmitters should use their own sender's (case) safety report unique identifier (A.1.0.1), but not changes the WWID.</p> <p>If the WWID is changed by MLM, this will cause the unnecessary nullification of numerous safety</p>	<p>purposes within EudraVigilance. This master will not be made available through the ICSR Export tool.</p> <ul style="list-style-type: none"> • If more than one (duplicative) individual case from the same or different sender organisations referring to the same literature record is identified in EudraVigilance, then a master case may already exist or will need to be created. For the literature case of the Agency's service, an ICSR will be generated with a MLM WWID. The WWID(s) of the duplicates already reported in EudraVigilance will be cross-referenced in the MLM ICSR in A.1.11 "Other case identifiers in previous transmissions". • The master case will be updated, which links all applicable ICSRs. • In this way, the marketing authorisation holder(s) is/are not required to nullify the individual case created in their safety database based on their own WWID and the marketing authorisation holder(s) can submit follow-up information where necessary using their assigned WWID e.g. to other regulatory authorities or contractual partners.

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	reports previously transmitted to other ICH regions, and may well not be acceptable to the agencies concerned.	
030	<p>Some results of the literature screening, as uploaded to the dedicated section of EudraVigilance, are not fully assessed (meaning that no exclusion criterion is allocated to some of the hits). This remains even for the screening sheets moved to the Archive.</p> <p>Could you please clarify the process?</p>	<p>Not all retrieved records will be reviewed on the day of screening. If this is the case, then they will be reviewed the following business day. The spreadsheet for the first day, when moved to the archive, will remain as it was when published.</p> <p>The archive is a record of the state of knowledge at a moment in time. Each sheet in the archive is not updated, but subsequent sheets have the following day's data.</p>
031	Are third parties who are contracted to provide literature monitoring services to MAHs within Europe able to access results on the EudraVigilance website?	<p>The restricted area of EudraVigilance is accessible to medicines regulatory authorities in the EEA and MAHs in the EEA.</p> <p>Third parties will have to ask their client with access to register them as a user.</p>
032	I am currently building and testing saved searches using the filter functions in the MLM export manager. Please could you help me to understand how the Active	<p>Within a given filter an OR operator is used by the system. So if you select the substance group PARACETAMOL and also the substance group CODEINE, then cases containing either paracetamol OR codeine will be returned.</p> <p>Between filters an AND operator is used by the system. So if you select the substance group</p>

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	substance group and Active Substance Combination fields are combined together using AND/OR operators?	<p>PARACETAMOL and the substance combination CODEINE HYDROCHLORIDE, then only cases with both paracetamol AND codeine hydrochloride will be returned.</p> <p>For the above reason, we do not generally recommend making single queries containing both a substance group and a substance combination. This would be best done via two or more different queries.</p>
033	Is it possible to use only Active Substance Combinations for filtering without entering any Active Substance Group?	Yes, this is completely possible and recommended when you require a substance combination (see question 32).
034	What will happen if the EMA identifies a case, which is subject to special situation (misuse, abuse, overdose etc.) without adverse reaction? Are they considered in that case to be valid ICSRs? And will they be processed by EMA?	Special situations without adverse reactions are retrieved in the searches and at screening are prioritized for assessment for follow-up, but they are not typically entered as ICSRs in line with Good Vigilance Practice Module VI section VI.B. 6 1-4 and the detailed guide regarding the monitoring of medical literature and the entry of relevant information into EudraVigilance database by the European Medicines Agency.
035	<p>It is noted that MAH's should continue literature searches not included by MLM. This could refer to two search activities:</p> <p>1. Searches of other data bases which may be appropriate for a product in certain territories but which are not included in the</p>	<p>Directive 2001/83/EC, paragraph 107(3) indent 3, states the following: "For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004, marketing authorisation holders shall not be required to report to the EudraVigilance database the suspected adverse reactions recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions". The requirements are further defined in GVP Module VI, chapter VI.B.1.1.2. "Literature reports": "The marketing authorisation holder should ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the medicinal product properties. In addition, marketing authorisation holders should have procedures in</p>

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	<p>searches conducted by MLM</p> <p>2. Searches of the same or similar data bases as the MLM search data bases, not for ICSRs but in order to obtain more general information on drug safety, such as epidemiological data concerning pregnancy risks, drug interaction studies.</p> <p>Please confirm if we are expected to continue searching one or the other or both criteria.</p>	<p>place to monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorisation, and to bring them to the attention of the company safety department as appropriate". For further information on what literature should be screened, refer also to GVP Module VI, chapter VI. Appendix 2 "Detailed guidance on the monitoring of scientific literature" and chapter VI .App2.2. "Where to look".</p> <p>In summary, MAHs need to continue to monitor all other medical literature not covered by the literature reference databases applied for the service by the Agency in accordance with Article 27 of Regulation (EC) 726/2004. This includes scientific and medical publications in local journals in countries where medicinal products have a marketing authorisation. For very specialised medical fields, for certain types of medicinal products or where safety concerns are subject to non-clinical research, marketing authorisation holders should establish the most relevant source of published literature for each product (see GVP Module VI, chapter VI.App2.2. "Where to look").The reporting obligations of suspected adverse reactions by marketing authorisation holders for the scientific and medical publications not covered by the Agency remain as outlined in GVP Module VI. Nevertheless, marketing authorisation holders need to continue to screen the scientific and medical literature to fulfil their other pharmacovigilance obligations e.g. in the context of preparing Periodic Safety Update Reports (PSURs) or Risk Management Plans (RMPs) as applicable. MAHs also have an obligation to screen the scientific and medical literature as a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues.</p>
036	<p>I can perform searches and requests for the ICSR, however, when I click on download, a pop-up with no content opens for a millisecond, but no file has been downloaded. Please advise how to download cases?</p>	<p>Please ensure you have applied the security setting as described in the User guide and that you have disabled any pop-up blockers:</p> <p>http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/05/WC500186798.pdf</p> <p>If it is not working on your computer, please try with a colleague's computer or a different internet browser, alternatively please speak with your IT department as it is likely that some configuration/security setting on your local computer is preventing the download.</p>

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037	I have created and saved my filters in the default html format. When I try to load these saved filters I get an error message.	<p>This problem is being investigated by the EMA.</p> <p>In the interim, when saving your filters add ".xml" at the end of the name and you will be able to load them.</p> <p>Any filters you have already created can be renamed to add .xml at the end and they will also work.</p>
038	<p>We have reached the stage of downloading the XML from EVWEB, however, In the XML, the MedDRA Version for all MedDRA coded elements is given as 'X', while it should be 'X.0'.</p> <p>Are you aware of this issue? Can it be corrected to X.0?</p>	<p>The EMA is aware of this matter as regards EVWEB and is investigating the impact of changing it so that the ".0" is displayed, since EVWEB is an integral part of many EMA systems, this will take some time. Please note that this does not affect MedDRA versions ending in ".1".</p> <p>In the meantime, there are two options to obtain cases displaying the MedDRA version as X.0:</p> <ol style="list-style-type: none"> 1. Download from the ICSR Export manager, where the cases have the MedDRA version as X.0 2. If you only need a single case, load it in EVWEB and you can view the XML file as submitted to EudraVigilance by double clicking the "Original message XML file" available from the "ICHICSR Message" field in the tree view. This opens up the case with the MedDRA version displayed as 18.0.
039	Are there any plans going forward to make additions to the top 400 chemical substance groups? If they are to be added to, when can we expect that to happen?	Currently there are no plans to extend the service to cover more than 400 active substance group however will review this situation again after 12-months of service operation.
040	In the document "Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period" it is described that MAHs should not report ICSRs subject to the	<p>As outlined in question 12, <i>Unless otherwise specified by national legislation and guidance</i>, concerned marketing authorisation holders should not submit the ICSRs resulting from the medical literature monitoring service to the concerned national competent authorities in the EEA.</p> <p>In practice, this means that as of 1 September 2015, MAHs should continue to transmit MLM ICSRs to the competent authorities of Germany, BfArM and the PEI, where required but not to any other EEA NCA.</p>

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	<p>medical literature monitoring conducted by the Agency to Member States in the EU/EEA Region, with the exception of Germany (BfArM).</p> <p>Could you please clarify to which Member States we should not report the ICSRs subject to the medical literature monitoring conducted by the Agency?</p>	
041	Do NCAs have access to the full articles ordered in the context of the EMA literature monitoring?	Due to international copyright laws neither the EMA nor the contractor can provide full text articles. These can be sourced using the document object identifier or URL provided in column G of the tracking spreadsheets.
042	Are MLM Service cases regarded as MAH or regulatory authority cases?	MLMSERVICE cases are processed as MAH cases, with the worldwide unique case safety ID entered in field A.1.10.2 (company number).
043	<p>The MLM ICSR Export function generates XML files containing multiple ICSRs. However, if only a single case is relevant for a company it might be more useful to download this single ICSR using the Query function in EV WEB Trader.</p> <p>We have tried to import such a</p>	<p>The MLM function within EVWEB shows the data exactly as captured within the EudraVigilance database, whereas the Export tool will update sections of the XML file as you have requested.</p> <p>In order to get the Message header section of the XML file populated from EVWEB, you can view the XML file as submitted to EudraVigilance by double clicking the "Original message XML file" available from the "ICHICSR Message" field in the tree view.</p> <p>You will still need to change the message receiver ID manually to match your own organisation ID, but all other fields will be populated in a manner to allow you to directly import the XML.</p>

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	single MLM XML export into the test environment of our database. Unfortunately the validation of that file failed as the message header is empty.	
044	Will MAHs receive through their EVWEB inbox or gateway the ICSRs inserted by MLM service related to the active substances contained in its owned medicinal products?	<p>The EMA's MLM service will not be transmitting ICSRs to MAHs. ICSRs are transmitted to EudraVigilance and NCAs and made available to MAHs via EVWEB and the EudraVigilance ICSR Export Manager.</p> <p>The information on how to retrieve ICSRs from EudraVigilance is provided in the User Manual on the dedicated EMA MLM Website.</p> <p>The Export manager allows you to filter on active substances, dates of transmission, country of occurrence and pharmaceutical form.</p> <p>The sum_icsr spreadsheet contains all identified ICSRs in progress, as well as all ICSRs pending follow-up from primary authors. To retrieve all MLM ICSRs in EudraVigilance since the beginning of the service a query should be run in EudraVigilance from for the start date of the service 01-Jul-2015 for all MLM ICSRs or using the Export manager.</p>
045	Following the update of the detailed guide for the MLM service, I have a question regarding the inclusion and exclusion criteria for processing of ICSRs. I note in the seriousness section of that particular document that non-serious case reports that occur outside of the	<p>This is correct. As of 1 May 2016 the MLM Service includes non-serious non-EEA cases as a result of feedback from MAHs</p> <p>In the spirit of reducing administrative burden and reducing duplication of efforts.</p>

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	European Economic Area (EEA) are now included in the process even though they are not required to be transmitted by GVP Module VI, chapter VI.C.4 "Reporting modalities". Is this correct?	
046	When reviewing the tracking sheets we often find that an article will appear more than once for different substance groups. Can these duplicate rows be removed?	<p>Every time an article is returned from the literature search for each substance group, it is recorded against that substance group and published in the appropriate spreadsheet(s). Each company has its own set of marketing authorisations and therefore each article is recorded for each substance group.</p> <p>To limit the spreadsheets to substances for which you hold marketing authorisations in the EEA or to remove duplicate references, the filter function of the spreadsheets should be used. Alternatively macro (a small program within Excel that automatically performs various simple steps on a spreadsheet) can be created. The format of the spreadsheets is the same every day, so the macro only needs to be created once and then it can be run on the spreadsheet every day.</p>
047	Are MAHs obliged to monitor the tracking sheets? If so, how often should they be reviewed?	<p>If you are continuing to perform literature searching in journals that the Agency is monitoring, you will need review the tracking sheets to avoid submitting duplicate cases. Alternatively, you can set up a filter or filters in the ICSR Export manager and run it/them periodically to download the cases related to substances for which hold marketing authorisations in the EEA.</p> <p>If the tracking sheets are used e.g. for reconciliation of cases with PSURs, a monthly cumulative tracking sheet published in the first week of the following month can be used. Presently (December 2016) it is published as a second spreadsheet in a daily download sheet.</p>
048	We are performing literature searching for a substance not covered by the MLM Service. We have identified a relevant article	<p>If there are no MLM Service substances that are co-suspect or interacting, then you should process the case and transmit it to the relevant Competent Authorities and/or EudraVigilance as applicable within the usual timelines.</p> <p>If your substance was co-suspect with one monitored by the MLM Service, then you should not</p>

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	<p>that comes from a journal monitored by the MLM Service. In this article, we have identified a case where only our substance (not covered by the MLM Service) is suspect. Should we process the case?</p>	<p>transmit that case to EV nor to EEA NCAs (unless they request such cases, see question 040). Instead you should notify the MLM Service desk (mlm@ema.europa.eu) and we will review the article and reply to you within 2 business days., If we agree that there is a case to be made, transmit it to EV within 7 days.</p>