12 May 2015
EMA/716877/2014
Inspections and Human Medicines Pharmacovigilance Division

Overview of comments received on 'Detailed Guide regarding the Monitoring of Medical Literature and the Entry of Relevant Information into the EudraVigilance Database by the European Medicines Agency on Literature Monitoring' (EMA/716877/2014)

From Stakeholder 01 to Stakeholder 16

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Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	SciencePharma, Monika Kosut, Pharmacovigilance Unit, Junior Specialist
2	Astellas, Bert van Leeuwen
3	Association of the Austrian pharmaceutical industry (PHARMIG), Michael Sander, Senior Advisor, Regulatory Affairs
4	Medicines and Healthcare products Regulatory Agency (MHRA), Rebecca Webb, Pharmacovigilance Inspector
5	Alliance Pharma PLC and Alliance Pharmaceuticals Ltd., Cleo Fu, Senior Pharmacovigilance Associate & Deputy EEA QPPV
6	Vigilex B.V. Sarah Davis, Senior Safety Executive
7	Gilead Sciences International Limited, Kelly Munnery, Regulatory Affairs Associate, International Regulatory Affairs
8	European Generic Medicines Association (EGA), Maarten Van Baelen, Medical Affairs Manager
9	Spanish Association of Pharmacists in Industry (AEFI), Cristina Nadal, Secretaria Técnica – AEFI – Sección Centro
10	Allergan, Dr Izabella Bossowska, EU QPPV
11	German Pharmaceutical Industry Association (BPI), Dr. Boris Thurisch, Geschäftsfeldleiter Arzneimittelsicherheit
12	Procter & Gamble, Sarah Champion, Global Safety Surveillance & Analysis
13	ZEINCRO Hellas S.A., Andreas Kourvetaris, Safety Manager, Safety Department
14	United Biosource (UBC), Myrto Ioannidi, Associate Director, Pharmacovigilance
15	European Federation of Pharmaceutical Industries and Associations (EFPIA), Sini Eskola, Director, Regulatory Affairs
16	Association of the European Self-Medication Industry (AESGP), Christelle Anquez-Traxler, Pharm, Regulatory and Scientific Affairs Manager

Stake holder no.	General comment/ Line number	Stakeholder comments	Proposed changes by Stakeholder, if any
1	General comment	Could you please specify what will be the next step for MAH after publishing Individual Case Safety Reports listings? Should all found ICSRs be entered into database of each MAH of the substance concerned and further analysed (signal detection)?	
1	Lines 100-102	Could you please specify whether MAH will be still responsible for the monitoring of studies other than Post Authorisation Safety Studies? It is stated, that the Agency monitoring service are excluded for suspected adverse reactions from interventional clinical trials. What should be done in case of lack of the information concerning status of the study?	
1	Lines 115-116	Which database will be used for this purpose (MedLine, PubMed, EMBASE, SCOPUS, EBSCO Publishing's Electronic Databases, SCIRUS etc.)?	
1	Lines 137-138	Please explain what do you mean by 'necessary additional search by trade name (in all their variants)'? In what kind of situation will it be taken into account?	
1	Line 157	Typographical error.	Proposed change: '…alternative identifier[5].'
1	Line 239	Could you please specify the electronic format of the ICSRs (xml, CIOMS etc.)? Will MAH be obligated to register all of the published results in its own databases (even if the name of the other MAH/product is provided)? Also, if the MAH/product is not provided, is MAH obligated to contact author of the article to specify it?	
2	Line 206	Will one attempt satisfy the requirements? And will this relieve the MAHs from their obligations?	
2	Line 241	A lisiting could be very long if a publication describes e.g. dozens of ICSRs. It would be practical to add a column with the number of ICSRs created and a box with EV case numbers. "The listing is provided on a daily basis". It would be more practical to also publish a cumulative list (per product/MAH) on the EV site.	
3	General comment	PHARMIG, the association of the Austrian pharmaceutical industry, would like to thank for the opportunity to comment on the draft detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency.	
3	General comment	We welcome and recognise the effort to simplify the monitoring regarding listed medical literature for the pharmaceutical industry and enhance the efficiency of reporting. However, as further outlined in the specific comments section below, there is still a considerable contribution of the industry required.	
3	General comment	Safety information from clinical trials (phase IV) is very often of particular interest but not provided by the Agency. Therefore, MAHs are still required to screen their substances themselves.	
3	General comment	MAHs are required to actively and regularly search in EudraVigilance for safety information related to their	

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		substances. It would be desirable to establish an alert setting where users could opt for being notified when new information on specified substances is available.	
3	Lines 89 – 93	The total number of substance groups to be included in the literature-monitoring services is depending on the allocated budget and may be subject to annual updates and changes by the Agency. Updates to the list of substances are being published in October each year becoming effective in January thereafter to allow MAHs a timely adjustment of their business processes in line with the substances being monitored by the Agency.	An annual interval for updates seems to be too long. We would recommend updates twice a year. Is it possible for MAHs to submit requests for amendments to the list of substances as it is the case with requesting substances on the EURD list by the MAH?
3	Lines 115 - 116	Non-indexed local journals are excluded from the Agency's monitoring activities and remain under the responsibility of the MAHs.	The established processes on monitoring and the respective resources in the industry have to remain in place even if the workload is reduced.
3	Lines 192 - 193	Individual cases related to purely non-serious adverse reactions, with a primary-source country outside the EEA are excluded from EudraVigilance.	The established processes on monitoring and the respective resources in the industry have to remain in place even if the workload is reduced.
3	Lines 206 - 207	One attempt to follow-up with the primary author(s) is made for serious adverse reactions based on a risk-based approach.	Industry is required to make more than one attempt to follow-up if important information is missing. Therefore, we suggest making at least two attempts.
3	Lines 241 - 246	A listing is provided to MAHs for ease of identification of applicable ICSRs at the EudraVigilance restricted website. The list contains the related substance(s) and substance group, the world-wide unique case identification number, the reference to the relevant literature reference including the DOI or URL or an	It would be desirable to establish an alert setting where users could opt for

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		alternative unique reference (if the DOI is not available), the primary source country, a seriousness flag as well as the receive date and receipt date to allow the determination the initial or follow-up status of the ICSR.	being notified when new information on specified substances is available.
3	Lines 256 - 258	A survey to be conducted at six monthly intervals of a sample of MAHs and national competent authorities in EEA Member States is to aid the identification of potential areas of improvement and to improve performance if required.	How is the sample of MAHs chosen? How is ensured that a representative sample of MAHs (for instance larger companies as well as SMEs) is included in the quality management process?
4	Line 71	Technically this is a partial service as MAHs are still required to perform global literature searches for the purpose of ongoing safety monitoring and non-ICSR safety data. Maybe the fact that MAHs are still required to search the literature for non ICSR data should be made explicit somewhere within the guidance – i.e. that this guidance applies only to the identification of ICSRs from the scientific literature.	
4	Line 192	With regards to the non-serious cases arising from outside the EU. Although exempt for reporting and entry into EudraVigilance MAHs will still need to include such cases in their ongoing safety monitoring activities and within PSURs. As these cases will not be available for download from EudraVigilance by MAHs what is the expectation for the identification of these types of cases by the MAH?	
4	Line 137	GVP Module VI, Appendix 2 indicates that searches should be performed taking into consideration alternative names such as numbers or codes used for products newly developed, chemical names, brand names, active metabolites. The statement from line 137 appears to be less explicit indicating that brand names would only be used where it is deemed necessary which does not necessarily reflect the GVP reference. It also does not define when it would be considered necessary.	
4	Line 206	For particularly important cases it may be useful to include the option for more than one follow-up attempt.	
5	General comment	The scientific literature screening and monitoring process carried out by the EMA will concentrate on ICSRs identification, so please confirm that the MAH is still responsible for screening the same literatures and active substances for the wider literature review required for PSURs and signals. If that is the case, would you suggest MAH to ignore ICSRs during the wider review or shall we keep a record for reconciliation with the listing published by the EMA. In any case, we understand that reporting to EMA is not required for ICSRs identified in the medical literature for the active substances that are monitored by EMA.	
5	General comment	What is the rationale of excluding entry of non-serious adverse reactions with a primary-source country outside the EEA? Is it due to reporting requirements? But surely the information is still considered an	

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		important source of signals?	
5	Section 4.1.4	Section 4.1.4 states “The ICSRs entered in EudraVigilance as a result of the scientific and medical literature screening activities are published daily in electronic format for download by MAHs.” Please provide further details on the electronic format, would this be an xml file? Is the idea for MAH to monitor the listing published by the EMA on a daily basis and download the appropriate ICSRs for database and signals evaluations? Further details on the MAH responsibilities will be greatly appreciated.	
6	Lines 89-93	If the number of substance groups included in the EMA’s literature search is dependent on the allocation budget, presumably there is the possibility that the number of substance groups being monitored could go down as well as up (this is not specifically excluded in the draft guide). If substance groups can be removed from the search, the guidance should state clearly how it will be decided which groups will be removed; this should take into account the numbers of Mas/MAHs associated with a substance group, since removing a substance group for which there are a large number of MAs/MAHs, would potentially then re-introduce duplication of effort for both the MAHs and for the Agency in terms of identification and processing of literature articles and identification of duplicate reports.	
6	Lines 117-119	While we would expect that any database searches would include all journals indexed in that database (rather than reviewing only selected journals within the database), this is not clear from the current wording and the situation needs to be clarified within the draft guide. The published list of medical literature included in the Agency’s search should also state clearly which databases are searched and that a database search covers all journals indexed in the database rather than just listing the journals being reviewed.	
6	Lines 166-167	What is the purpose of the planned publication of the search results on the EudraVigilance website? With the information being made available, will MAHs then be expected to access/review this information routinely? If there is an expectation for action from the MAH, this should be included in the guidance.	
6	Lines 190-192	It is not entirely clear from the wording but it seems to suggest that the start of entry of non-serious cases into EudraVigilance may not coincide with the start of the EMA performing literature searches. If there is a period when the EMA is performing literature searches and not entering the non-serious cases into EudraVigilance, what are the obligations for MAHs for these non-serious cases? For instance, would MAHs be expected to identify such cases, enter them into their databases and report to the EMA – or will the EMA identify the cases from the literature search and then enter them into EudraVigilance at a later date, with no obligation for the MAH in the interim period?	
6	Lines 216-217	The wording suggests that it is acceptable (or even expected) for the MAH to follow up for additional information from literature articles outside the Agency's follow up process. While this is appropriate, it will be important for MAHs to understand how the EMA’s follow up process works; for instance, will there be any integration between RMPs and follow up (for instance, where the MAH for a product is required to follow up cases of a particular event for specific information, can the EMA be informed of this requirement so that literature cases can be followed up in the same way). Alternatively, will the follow up tracking table referred	

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		to in line 212 be made available to MAHs so that they are aware which cases are being followed up? If the MAH and EMA follow up processes operate entirely independently, there is the potential for duplication of effort if both parties follow up with the author.	
7	Lines 44-46	To avoid confusion and aid clarity please could the text be amended to reflect that the Agency monitoring pertains to generic products rather than innovative products	The Agency shall monitor selected medical literature for reports of suspected adverse reactions to generic medicinal products containing certain active substances as defined in the published list
7	Lines 52-57	Clarity on expectations regarding generic marketing authorisation holders (MAH) expectations re searching vs. reporting, but also the scope of nature of the EMA search coverage needs to be determined given that in some Individual Case Safety Reports (ICSR) searching is still required. What is the EMA to use and will the EMA offer a service for MAHs to check if relevant journals are already covered by the EMA search – how will this be known?	The MAH of those generic medicinal products containing certain active substances as defined in the published list for which the Agency assume ICSR identification and recording in Eudravigilance. The MAH should still monitor selected medical literature for reports of relevance to signal detection activities. In addition, relevant medical and scientific literature not within scope of the EMA search should still be performed by the MAH for identification of ICSRs. Guidance re how MAH knows what is covered is required

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7	Lines 83-93	See comments relating to rows 44-46.	
7	Lines 89-93	Text implies if there is not sufficient budget the EMA may revert to searching by the MAH – this seems unreasonable and inefficient to have to annually monitor and include or exclude based on budget limitations of EMA.	
7	Line 110	Knowing the databases will be essential for the MAH to know if relevant journals are covered and as above – will the EMA support confirmation of availability to the MAH upon request?	
7	Line 124	GVP Module VI requires weekly literature searching whereas this implies daily is required – please clarify why this has changes in the EMA proposal?	
7	Line 153	Please clarify what will be assumed as day zero for entry into database by EMA and what day zero will be for the MAH when the MAH access the report (when such accessibility is available) to meet worldwide regulatory reporting expectations.	
7	Lines 166-167	Please clarify the intent of making the search results available – what is the expectation of the EMA of the MAH?	
7	Line 179	Please clarify if there is a drug and event that these will still be included in the database as this would be expected for the MAH to have availability for signal detection activities or will they be sent to the MAH via another route? 4.1.4 implies all such reports with missing valid criteria will be followed up – is this correct?	
7	Line 186	Industry usually has to take the date of the receipt of the search outputs as day zero not the date valid cases were identified. What is the time between running a search and reviewing the output – this should also be included.	
7	Line 190	Please clarify – a literature non-serious ICSR from a US publication will be excluded from the EMA identification and entry? Will serious non-European Economic Area (EEA) be entered? Therefore it needs to be clearer that any non EEA non serious will be exempt from this process and needs to be managed by the MAH, which will result in duplicate work.	
7	Lines 203-212	Please clarify: regardless of risk based approach, only one follow up will be performed by EMA? Do the MAH have access to the follow up tracking table?	
7	Line 216	If the MAH is not searching it is assumed this refers to where a reporter send a case in addition to a literature article being generated – otherwise it could be confusing if an MAH and the EMA are performing follow-up on the one article – could this be clearer? If the EMA identifies an ICSR that was already in a MAH database – does the EMA wish to be advised so they can merge cases? Clarity where the EMA has identified a case in the literature should not be followed up by an MAH would be helpful to avoid duplicative follow up attempts when data is received from EMA.	
7	Line 238	How will the EMA make the data available to the MAH? If this is just the search output vs. the processed case – what is the expectation of the MAH re the search output as making MAH aware of this data in the search output could result in worldwide obligations to start processing and forwarding to worldwide	

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		authorities? The purpose of receipt of this output is unclear vs. a processed case.	
8	General comment	The EGA welcomes this opportunity to comment on the draft Detailed Guide regarding the Monitoring of Medical Literature and the Entry of Relevant Information into the EudraVigilance database by the European Medicines Agency. Although we fully understand and support the intention of the proposed guideline, the EGA members have a few comments to make.	
8	General comment	EGA would like to emphasize that Marketing Authorisation Holders should be able to receive the ICSR from literature directly in xml according to the entries in the EudraVigilance database, in the same way as reporting to the Competent Authorities is done. We are aware that this will only be an option at a next stage but would like to include this for the first upgrade of the system.	
8	Lines 123-131	These lines contain a description of reports that will be identified in the literature search. This is actually a repetition of what is described in lines 98-109 but in this section additional types of cases were added: "reports of single or multiple cases of suspected adverse reactions from organized data collection systems referring to registries, post-approval named patient or compassionate use ". This should also be added to lines 123-131.	
8	Line 135	“App2.3 'Database Searches' and are being customised…” This sentence is not clear. Shouldn’t it be “App2.3 'Database Searches' ~~and~~ are being customised…”	This sentence is not clear. Shouldn’t it be “App2.3 'Database Searches' ~~and~~ are being customised…”
8	Line 157	delete ”5” after ”identifier”	delete ”5” after ”identifier”
8	Lines 158-161	Will the criteria for inclusion/exclusion be made available to all stakeholders? It is important that the criteria are previously and rigorously defined prior to the implementation of the literature monitoring.	
8	Line 239	The possibility for the MAH to download a batch of XMLs instead of an individual XML.	
8	Line 241	The possibility for the MAH to perform queries on the listing provided to the MAH.	
9	Lines 210-211	Maybe this explanation about IME is not under the correct section (4.1.2. Follow-up of individual cases related to suspected adverse reactions identified as a result of the scientific and medical literature screening activities).	
9	Lines 232-234	Are the copies of the articles to be accessible to MAH?	
9	General comment	We miss a section that describes how the MAH has to proceed when a literature case is detected and this case has also been detected by EMA. The instructions for MAH for Spanish literature cases given by the AEMPS are very clear “ REPORTS OF SUSPECTED ADVERSE REACTIONS FROM THE LITERATURE: INFORMATION FOR THE PHARMACEUTICAL INDUSTRY” https://sede.aemps.gob.es/en/usoHum/farmacovig/docs/Instrucciones_notificacion_RAM_Literatura.pdf	
9	General comment	We miss a section describing how the MAH has to proceed regarding the ICSRs on literature that are provided by the EMA, Has the MAH to populate all these ICSRs in its Pharmacovigilance Database? Has only	

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		to populate the ICSRs that can be attributable to the MAH? In case the ICSR can be discarded from being from the MAH (eg: due to the country of occurence, presentation of the pharmaceutical form), Or can consider to mention the ICSRs in the PSUR.	
9	General comment	"As the European Union's (EU) pharmacovigilance legislation has given the EMA responsibility for the monitoring of scientific and medical literature for a defined list of active substances used in medicines, the Pharmacovigilance group of AEFI considers important to include in the guide a section specifically stating that the Marketing Authorization Holders are exempt from monitoring the medical literature for the products that the EMA will review.	
10	Line 38	Whilst the proposal may/will reduce the number of duplicate reports to Eudravigilance, duplication will continue elsewhere globally. In fact, it could be argued that the enhanced process in the EEA will increase the number of duplicate reports to eg the FDA since the literature review will have been performed more thoroughly than in the past. Has collaboration with other ex-EEA agencies been considered?	
10	Line 96	Please clarify exactly what is considered a 'conference proceeding'?	
10	Line 97	What media will be searched? What will be considered a 'media release'?	
10	Line 101	Since this information will need to be captured by the Company, can it be inferred that although the Agency shall monitor selected medical literature, this monitoring will need to be repeated by the Company to capture the ADRs from interventional clinical trials?	
10	Line 143	Does limiting to title or abstract really increase search precision?	
11	General comment	This guide describes the procedure and technical aspects of monitoring scientific literature databases by the EMA for any suspected adverse reactions and other safety relevant information related to selected active substances/substance groups. The benefit as well as reduction of costs and manpower of MAH mainly depends on selection criteria of active substances for which EMA fulfills monitoring. The MAHs shall not be required to report to the EudraVigilance database the suspected adverse reactions recorded in the listed medical literature. But the obligation and the burden of MAH to screen for local not indexed articles for selected substances still remains. Also the obligation for MAHs to screen all other not selected medical literature still remains. Probably companies with generic focus and well known and established active substances will benefit from medical literature service of EMA, while (smaller) companies with niche products will not have advantages.	
11	Section 1.1,	The risk of duplicate reporting is relative since reporting obligation is not applicable if brand is specified, ownership could excluded, literature that originate in a country where a company holds a marketing authorisation but has never commercialized the medicinal product etc. Furthermore the obligation for MAH is not only to monitor but also to report cases if applicable.	(Lines 36-41) Currently, for active substances included in more than one medicinal product for human use, literature cases **could be** reported

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			in adverse reaction case reports in a duplicative way by marketing-authorisation holders (MAHs) in the European Economic Area (EEA), which is based on their obligation to monitor **and to report if applicable** scientific and medical literature as outlined in the Good Pharmacovigilance Practices (GVP) guideline, Module VI 'Management and reporting of adverse reactions to medicinal products'…"
11	Section 1.1	In many cases there is more than one suspected drug. It will frequently happen that one of the suspected drugs is monitored by the EMA, the other(s) not. As a MAH of a suspected "non-EMA drug", am I obliged to check if any of the cosuspected drugs is on the list of EMA-monitored drugs? And if one of the co-suspect drugs is on the list, shall I report or wait for EMA to publish that case? From national authorities we know that reporting can be delayed (especially during holidays)…	In case of more than one suspected drug of which one is on the EMA's list of substances, the MAHs of the non-listed drug(s) shall not be required to report to Eudravigilance database.
11	Section 1.2 and Section 5	Obviously there are selection criteria for appropriate service provider (including the price). It should be noted that according to experience it is important that staff who conducts the search should have detailed and comprehensive knowledge about active substance and it´s pharmacological profile, use patterns etc. to avoid oversight of relevant articles.	
11	Section 2.1	"High number of MAHs" should be specified or at least minimal criteria should be given.	
11	Section 2.2	It should be mentioned in the context that according to GVP module VI literature articles, which summaries results from post-authorisation studies were excluded from reporting obligation. This type of literature article describes 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, and aggregated	

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		data on patients are often presented in tables or line listings. The main objective of those studies is to detect/ evaluate specific risks that could affect the overall risk-benefit balance of a medicinal product.	
11	Section 3.1	Is there any possibility for MAH to have influence on search term construction to optimize the search? According to usually long term experience of MAHs with appropriate search terms for their products/active substances a participation of MAH would be effective.	
11	Section 4.1.2	Are there any possibilities of MAH to be integrated in follow-up process. Depending on diverse circumstances the follow-up information which seems to be relevant for individual MAH could be very different. Further, the risk-based approach mentioned in line 207 is not specified.	
11	Section 4.1.3	It would be of major importance, that the copies of the articles are also accessible to MAHs.	(Line 232) The copies of the articles are accessible in the literature repository to the national competent authorities and the MAHs in EEA Member States.
11	Section 4.1.4	Hopefully the electronic format means the current E2B ICSR format? The ICSR should be available as CIOMS form and as xml-file - as it is the case on the website of the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM). From view of MAH it would be important that the ICSR generated on the basis of this literature search by the EMA will be accessible for downloading in an importable format (E2B) by the MAH. This would ensure an effective and cost-efficient processing of ICSR by the MAH in their database and would be one important basis for safety concerns, as preparing PSURs or Risk management plans. The opportunity for electronically downloading in an appropriate format should be clearly stated in section 4.1.4.	(Line 238) ICSRs entered in EudraVigilance as a result of the scientific and medical literature screening activities are published daily in electronic forma (E2B(R2) ICSR format (xml-file) and CIOMS I form) for download by MAHs.
11	Section 4.1.4	According to 4.14. ICSRs are published daily by the EMA. MAHs are obliged to screen literature at least weekly according to GVP Module VI. We assume that weekly screening of Eudravigilance by MAHs is sufficient. Please confirm.	
11	Section 5	The approach to consult stakeholders via surveys as regards the functioning of this new process is very welcomed. Consideration might be given to the selection of MAH to be approached. It should be a group representing the different organizations, i.e. large, medium and small enterprises as well as companies with focus on research & development, generics, vaccines etc. or prescription vs. OTC products. Perhaps involvement of the relevant stakeholder organizations like Eucope and others would be beneficial.	
12	Lines 4-6	Correction of name of document to more accurately reflect content	DRAFT detailed guide regarding the monitoring of scientific and medical

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			literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency.
12	Line 80	Correction of title to more accurately reflect content and for consistency.	Monitoring of selected scientific and medical literature for reports of suspected adverse reactions.
12	Line 117	Change wording to more accurately reflect content and for consistency	The Agency publishes the list of the scientific and medical literature with the name, type and short description of the journal/reference database(s) as well as the number and the names of the journals covered by the Agency's services.
12	Lines 117-119	Where will the list of the scientific and medical literature be published?	
13	Lines 133, 239-240	“Daily refers to calendar days with the exception of weekends”	“Daily refers to business days”
13	Section 2.2.i., 3.1.	Section 2.2.i contains fields, which are repeated in section 3.1., out of which the first and the third bullet points of section 3.1., are identical with the first and fourth bullet points of section 2.2.i. The second bullet point of section 3.1. slightly differs from the second bullet point of section 2.2.i., as well as the third bullet point of 2.2.i is completely missing from section 3.1.	This is confusing for the readers and we propose harmonization of the references to the 2 sections (2.2.i, 3.1.), or cross reference of one section to another.
13	Line 71	“Avoid partial service that would necessitate duplicative efforts by MAHs” According to the reference VI.C.2.2.3. of GVP Module VI “As regards the screening of the scientific and medical literature, the requirements provided in this Module are part of the wider literature searches which need to be conducted for periodic safety update reports”, the review of the International literature shall include the “wider literature searches which need to be conducted for periodic safety update reports” as to	We propose the 3.1 Screening of selected scientific and medical literature to be adapted as to include “wider

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		avoid duplicative efforts. This is not included in the current guide, as detailed in 3.1, and this will result to duplicative efforts, since the MAHs will have ultimately to perform international literature review, for the "wider literature searches which need to be conducted for periodic safety update reports".	literature searches which need to be conducted for periodic safety update reports". The results of this "wider literature searches" shall be also reported in addition to Results of individual cases.
13	Line 97	"media releases or similar products" The phrase "similar products" is vague and unclear to the readers.	"media releases or similar sources "
13	Line 98	"For the purpose of the identification and retrieval of any new information on:" Regarding the phrase "new information", this could be interpreted as excluding the re-publications, while this is not clarified in GVP Module VI.	
13	Lines 98, 110, 113	The Latin numeration in these lines is not correct, as line 98 should have been marked with i), line 110 with ii) and line 113 with iii)	
13	Line 115	"Non-indexed local journals are excluded from the Agency's monitoring activities and remain under the responsibility of the MAHs" By referring to "non-indexed local journals" that "remain under the responsibility of the MAHs", a misunderstanding may arise that the MAHs shall only review "non-indexed local journals" whilst MAHs shall also review abstracts from local meetings and draft manuscripts.	
13	Line 157	"alternative identifier5"	"alternative identifiers"
13	Lines 107-108, 129-130, 162-163	"use of a medicinal product during pregnancy or breastfeeding" According to GVP Module VI, section VI.B.6.1.b "Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk should be reported in accordance with the criteria outlined in VI.B.7." Therefore the use of a medicinal product during breastfeeding is not a situation that the GVP Module VI requires.	"use of a medicinal product during pregnancy or suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk"
13	Line 192	"purely non-serious" The word "purely" is confusing and vague	"non-serious"
13	Line 193	"a primary-source country outside the EEA are excluded from Eudravigilance" The GVP Module VI, refers to EU and not to the EEA. A uniformity shall exist amongst the guidance documents.	"a primary- source country outside the EU are excluded from Eudravigilance"

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13	Lines 206-207	“One attempt to follow-up with the primary author(s) is made for serious adverse reactions based on a risk-based approach. This refers to individual cases, where the outcome is not known” According to the lines 206,207, follow up attempts will be made for serious adverse reactions, while according to GVP Module VI, section VI.B.3. it is clearly stated that “This is particularly relevant for monitored events of special interest, prospective reports of pregnancy, cases notifying the death of a patient, cases reporting new risks or changes in the known risks. This is in addition to any effort to collect missing minimum information (see VI.B.2). Any attempt to obtain follow-up information should be documented.” We propose:	“One attempt to follow-up with the primary author(s) is made for prospective reports of pregnancy and cases notifying the death of a patient. For other serious adverse reactions, one attempt to follow-up with the primary author(s) is made based on a risk-based approach. This refers to individual cases, where the outcome is not known”
13	Lines 208-209	Current reference: [follow-up will be performed] “for serious cases where not all of the minimum reporting criteria are available” A follow up is meaningful only when the identifiable patient criteria is missing, therefore we propose rephrase to: “for serious cases where the identifiable patient criteria is missing”. However, this should be included in the process until the identification of an individual case and not under the 4.1.2 which refers to follow-up of individual cases. We also propose to be clarified what will be the procedure for the cases where identifiable patient criteria is still missing after the one follow-up attempt (i.e. will these “incomplete”cases be then visible from MAHs?)	
14	General comment	UBC would like to congratulate the initiative of developing this guide that will provide a significant support for the elimination of duplicate reporting from multiple MAHs. The impact of the implementation of this Guide will, however, be even greater for MAHs that do not have the resources to perform a direct reporting from their database and that, presently, are required to perform data entry of the Individual Case Safety Reports in EVWEB after performing all the case processing activities in their own database.	
14	Lines 186-189	The paragraph mentioning the definition of day zero should also include the mention of the Day zero for an ICSR retrieved in an abstract, to be aligned with the definition in the GVP Module VI App 2.7	To add the sentence “day zero for a reportable adverse reaction present in an abstract is taken to be the date on which the search was conducted”.
14	Line 144	In order to guarantee that the results obtained in the searches performed are reproducible, the date used as	A sentence could be

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		search criteria should be the “date of creation” or “Added date”, since in some databases, the use of publication date may not be accurate if the article is added to the database long after the publication date.	added to the text to precise that the search will be done using the “date of creation” or the “Added date”.
14	Lines 274 and 283	It is not clear from the document whether the electronic copies of the literature articles will be made available to the MAHs as well. Will that be case? If yes, how will be the copyright issues managed, especially in the second phase described in the document?	Clarify in the text if the MAHs will have also access to literature articles and how the copyright issues will be managed.
14	Line 133	The text in line 133 very distant from the information that it refers to.	The text in Line 133 should be incorporated in line 124.
14	Line 142	Space missing	“abstractor” should be replaced by “abstract or”.
14	Line 157	Reference formatting	The number 5 in line 157 should be formatted as superscript.
15	General comment	EFPIA welcomes this guidance which provides clarification on the process for agency monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the EMA. We note that although entitled detailed guidance, this document is high level and further information will be needed before a full impact analysis can be made. After extensive review of this current draft, the following high level points have been identified (with detailed comments in the tables below. Many of these points in EFPIA’s opinion will require MAHs to add complex new processes whilst still screening the same product/ journal combinations, thereby increasing MAH workload and being contrary to the key principle of ‘Avoiding a partial service that would necessitate duplicative efforts by MAHs’.	
15		Questions/Concerns based on current text: 1. Process for duplicate checking /reconciliation – will the service provider have appropriate access to EudraVigilance (EV) for duplicate checking against ICSRs submitted pre-publication? 2. Reconciliation – MAHs must duplicate check against their database at download, the efficiency of which will depend on degree to which ICSRs have been privacy redacted (see detailed comments 177-246) 3. Exclusion of Non-Serious ICSRS for transition period, plus exclusion of non-serious from outside EEA - MAHs will have to screen same literature for the non-serious, plus exclude serious for given product/journal from EV submission	

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		4. Exclusion of Interventional Clinical Trial ICSRs - to avoid MAH having to screen same literature 5. Definition of suspect – clarification needed re: inclusion/exclusion if reporter states 'probably not related' in article 6. Process for flagging of aggregate articles with no individual identifiable ICSRs – or MAHs would still need to screen same journals for PSUR inclusion 7. Determination of 'Off Label Use' – only if so stated by reporter? 8. Transparency, frequency of update of search criteria – no mention of access by MAH to search criteria, including process for trade names as well as generic 9. Follow-up process – further define level of follow-up/ potential overlap with MAH obligations, i.e. where RMP commits to targeted questionnaires to reporters, who will be responsible (serious and non-serious) 10. Retransmission outside of EEA – propose Guidance states that, per ICH E2B A.1.6, the MAH should use the day they first received the information from EV as Day Zero	
15		Missing Information: 11. Process for inclusion/exclusion of articles on combination products – i.e. where one of the combination products is on screening list but not the other (risk of neither party or both entering) 12. Suspected transmission of an infectious agent – such ICSRs required per GVP but not mentioned in current draft 13. Screening for articles meeting 'Special Situation' criteria – or as per GVP MAH will still need to screen same product/literature combinations to identify these 14. Reference to excluding articles by agencies and meta-analysis - i.e. exclude 'already reported' and 'republished data' 15. Process if an MAH disagrees with decision on inclusion/exclusion criteria for a given article – i.e. if excluded but still considered reportable to agencies outside EEA and/or needed in database for signal detection 16. Process defining how/when concomitant medications within an article will be handled - i.e. would they ever be 'upgraded' to suspect? 17. Details on access and format for down-loading ICSRs – i.e. what access restrictions will apply (e.g. only MAH or allow for Business Partner of MAH), technical aspects (add XML) 18. The actual implementation date is unclear - clarity would aid MAH preparation	
15	Lines 82-93 and Lines 94-120	Regarding the list of active substances and literature to be monitored, will the MAHs have the opportunity to comment on/suggest amendments to the list? Clarification needed of how ICSRs will be handled when AEs are implicated with multiple substances in the article	Proposed change: Confirm MAHs will have opportunity to comment on list of active substances and literature Required outcome:

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			Literature - MAHs will have the opportunity to comment on the list of active substances and literature that the agency is monitoring, if applicable.
15	Lines 94-120	It seems the Agency will not screen for special situations, i.e. Information on non-human data that are relevant for human safety; Drug exposure during pregnancy with normal birth outcome ; Suspected adverse reactions from interventional trials that are published	Proposed change: Clarify how this will be achieved without the MAHs duplicating the screening of the journals already screened by the Agency Required outcome: Special Situations - Avoid Duplication of effort /compliance
15	Line 100	The draft guidance as well as GVP module VI doesn't clearly specify when multiple cases should be created rather than single cases.	Proposed change: To add:- Multiple cases of suspected adverse reactions will be created when there isn't one single identifiable patient characterised by initials, patient identification number, date of birth, age, age group or gender. Required outcome: Aggregate Data - We recommend to provide a position and to update these documents in order to ensure consistency in the data entry process
15	Lines 100-109	Will the agency perform duplicate checks against EV to ensure case not previously reported by MAH during	Proposed change: Perhaps

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		the actual study? Will the agency also do a duplicate check to ensure not a case previously submitted as a solicited report from the MAH at time event occurred during the program?	the Agency could suggest a mechanism or processes to help MAHs with duplicate identification. Required outcome: Duplicate Checks - Ensure clarity, without which we perceive a risk of creating duplicate ICSRs with different WWCIDs.
15	Lines 100-109	Will it be the agency itself or it's vendor who is responsible for conducting follow up with the corresponding author for missing information as the MAH does now? If vendor, what degree of training will be required/provided?	Required outcome: Follow-up - Process clarity
15	Lines 100-109	We recommend specifying that suspected adverse reactions related to investigational or auxiliary medicinal product, or concomitant medications will be excluded. The guidance provides no recommendation regarding the ICSRs identified in publications with aggregated review of several publication or metadata analysis. We recommend they should be excluded as “republished data”.	Proposed changes: reports of single or multiple cases of suspected adverse reactions from studies including post-authorisation study results (with the exclusion of suspected adverse reactions from interventional clinical trials related to investigational or auxiliary medicinal product, or concomitant medications,); Add after line 109: Report of single or multiple cases of suspected adverse reactions published in review articles and

Stake holder no.	General comment/ Line number	Stakeholder comments	Proposed changes by Stakeholder, if any
			metanalysis will be excluded. Required outcome: Exclusions - Process clarity
15	Line 101	By excluding suspected adverse reaction from interventional clinical trials from this literature monitoring service is adding MAH burden.	Proposed change: As this exclusion leads to re-review by MAHs, we propose this exclusion to be removed Required outcome: Exclusions - Avoid duplication of effort
15	Lines 103-106	Wording in section 2.2 is not repeated in section 3.1 (i.e. there are 4 bullets in section 2.2, should these all be repeated in section 3.1 where only 3 bullets appear)	Required outcome: Alignment - Harmonisation between sections 2.2. and 3.1
15	Line 103	According to GVP module VI, literature ICSRs which are based on an analysis from a competent authority database within the EU should be excluded.	Proposed changes: reports of single or multiple cases of suspected adverse reactions from organised data collection systems referring to registries, post-approval named patient or compassionate use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers and information gathering on efficacy or patients' compliance, excluding literature ICSRs

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			which are based on an analysis from a competent authority database within the EU. Required outcome: Exclusions - Process clarity
15	Lines 107-109 and Lines 129-131	Suspected transmission of an infectious agent via a medicinal product is omitted. Per GVP module VI these are reportable in 15 days and are important medical events.	Proposed change: Add to sections starting line 107 and 129. Required outcome: Suspected Transmission - Avoid duplication of effort
15	Line 111	Please confirm that the scope of the medical literature is not restricted to the publications from the EU/EEA.	Proposed change: “The scope refers to widely used and daily updated scientific and medical literature reference databases including literature from EU and non-EU countries in line with those referred to in GPV module VI” Required outcome: Literature Scope - Process clarity
15	Line 115	Local journals may be indexed in non-international databases, this should be more clearly specified.	Proposed change: Local journals non indexed in international databases are excluded from the Agency’s monitoring activities and remain under the responsibilities of the MAHs.

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			Required outcome: Local Literature - Process clarity
15	Line 119	Re “changes published in Oct and effective in January to allow MAH to adapt”, If the substance list is reduced significantly, MAH’s may not have time to prepare.	Proposed change: That the EMA provide additional notification to MAH’s if there will be substantial changes to the substance list Required outcome: Search Criteria - Transparency/compliance
15	Line 126	The qualification of an adverse event as an adverse reaction implies an assessment of the causal relationship, cf. GVP VI B.2 (validation of reports): "If the primary source has made an explicit statement that a causal relationship between the medicinal product and the adverse event has been excluded and the receiver (CA or MAH) agrees with this, the report does not qualify as a valid ICSR since the minimum information is incomplete". Whether the receiver agrees or not with the exclusion of the causal relationship depends on the expertise of the receiver regarding the active substance.	Proposed changes: Clarify how the Agency will ensure the Service Provider has the adequate expertise for all the active substances that will fall in the scope of their activities? Or will the Provider screen and enter all adverse events? Required outcome: Assessment - Process clarity
15	Line 130	We acknowledge that situations of off-label use will be identified by the agency. However the criteria used to identify the off-label use situations are not detailed in the guidance. Knowing that the same product may be approved by several MAHs for different indications, we recommend the off-label use situation to be identified only if a situation of off-label use is described in the article. We recommend both MAH and EMA to follow this rule.	Proposed changes: “as well as off-label use (as reported by the author), misuse, abuse overdose…” Required outcome: Off-label Use - Process clarity/compliance
15	Line 132	Re: “The screening includes all suspected serious and non-serious adverse reactions...”, will the EMA explicitly search for a specific causality in each article?	Required outcome: Causality - Process clarity

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15	Lines 137-138	To comply with the worldwide regulations it is required to take all international trade names into account.	The substance groups search has to be exhaustive, where necessary additional search by trade name (in all their worldwide variants) is also to be taken into account. Required outcome: Search Criteria - Process clarity/compliance
15	Line 140	How will the Agency manage the screening of articles that are not yet indexed when they are introduced in the literature databases? Search criteria based on indexation will not retrieve these articles.	Required outcome: Search Criteria - Process clarity
15	Line 141	Does "The search is performed at full text level" mean that searching the full text article or the "full text" of the reference from the commercial database (i.e., only the title, author abstract, citation, and indexing)? GVP Module VI requires the MAH to review the full-text article; the services should do the same since adverse events are often not mentioned in the abstract.	Proposed change: The search is performed at full text level Required outcome: Search Criteria - Process clarity
15	Lines 141-143	Will the agency be entering all articles reviewed, including those considered not reportable or non-valid? or only those with identified ICSRs? Will the Agency be sharing the literature case creation conventions with MAHs, including the criteria for excluding/including literature reports for further case processing? What if an MAH perceives an article differently than the agency?	Please provide clarification Required outcome: Assessment - Process clarity/compliance
15	Line 144	Will the MAH have access to the audit report?	Required outcome: Access - Process clarity
15	Lines 145-149	Knowing that the database to be used is not defined in this guidance, we recommend to specify that search constructions should be revised and updated if needed, each time a thesaurus update is released.	Proposed changes: Search constructions are routinely updated and maintained where necessary to improve search precision and to align with any updates to the thesaurus used for

Stake holder no.	General comment/ Line number	Stakeholder comments	Proposed changes by Stakeholder, if any
			indexing as well as to the substance groups as referred to in chapter 2.1. Updates are announced in due time by the Agency. Required outcome: Search Criteria - Process clarity
15	Lines 158-161	What methods will the EMA provider use for translation of articles? Are they validated? Where an article is in a foreign language, will the agency translate into English and make text available to MAH?	Required outcome: Translation - Process clarity
15	Lines 166-167	It is unclear what would be included in the search results that are published daily. By way of sample explain how this will differ from the published list of ICSRs entered into Eudravigilance as per lines 238-246.	Proposed change: Suggest rewording "Search results based on the execution of scripts are made publicly accessible on a daily basis and will include the above referenced data to allow the MAHs to identify if any ICSRs for their products have been identified from the search". Required outcome: Published Lists - Process clarity
15	Lines 166-167	The outputs are provided in a tabular, user-friendly format on the EudraVigilance restricted website. Who has access to this website to review these uploads on a daily basis, noting that many MAHs have Business arrangements that must be addressed i.e. by what process can an MAH arrange ICSR access by a Business Partner?	Proposed changes: The outputs are provided in a tabular, user-friendly format on the EudraVigilance restricted website which is accessible to the MAHs as applicable Please confirm the

Stake holder no.	General comment/ Line number	Stakeholder comments	Proposed changes by Stakeholder, if any
			registration process to have the ability to download ICSRs from Eudravigilance Required outcome: Access - Process clarity for access to the restricted website.
15	Line 168	Will “records of literature searches” be accessible to MAH?	Required outcome: Access - Process clarity
15	Lines 177-246	Will the EMA be applying any PII data for the ICSR’s downloaded from Eudravigilance that may inhibit duplicate checking by the MAH? If yes, can the EMA provide the parameters of PII date exclusion?	Required outcome: Data Privacy - Process clarity
15	Lines 182-185	This suggests the Agencies day zero should be used for the MAH if the ICSRs are re-transmitted to outside EEA agencies. However per ICH E2B “When retransmitting information received from another regulatory agency or another company or any other secondary source, A.1.6 is the date the retransmitter first received the information.”	Proposed change: Suggest insertion at end of row 189 “In case of retransmission outside of Europe, MAH should use the date they first received the information as day zero.” Required outcome: Clock Start - Process clarity/compliance
15	Lines 190-192	Please clarify that for cases that include serious and non-serious reactions, they would all be entered into the same ICSR and be made available to the MAH. i.e. avoiding partial inclusion from a single literature article	Required outcome: Non-Serious - Process clarity/compliance
15	Line 192	It would be helpful to confirm that all serious or special situation cases (see lines 107-109) are recorded even if they occur outside the EEA.	Proposed change: However, all other new information as described in chapter 2.2 is entered in Eudravigilance even if from outside the EEA.” Required outcome: Outside EEA - Process

Stake holder no.	General comment/ Line number	Stakeholder comments	Proposed changes by Stakeholder, if any
			clarity
15	Line 194	More clarity should be provided on the quality standards of data capture i.e. the intention of the author should primarily be followed with regards to both the adverse reaction terms to be captured and also with regards to a suspected causal relationship with the products in question. Unless this happens, literature articles may trigger the processing of many incidental events. Also events may be captured for which the author did not suspect/ mention any causal relationship with the product in question in their article	Required outcome: Incidental Events - Process clarity
15	Lines 195	According to GVP VI.C, the following articles can be excluded from reporting of ICSRs by MAHs: - literature ICSRs which are based on an analysis from a competent authority database within the EU. - literature articles, which present data analyses from publicly available databases or, which summarise results from post-authorisation studies However, MAHs need to collect these articles for sake of signal detection. Will they be reported by the Agency to the MAHs?	Required outcome: Exclusions - Avoid duplication of effort/compliance
15	Lines 203 and 216	EMA criteria for follow-up appears to be less stringent than that expected of MAH, e.g. where MAH has a targeted questionnaire (serious and non-serious) in an RMP?	Proposed change: Suggest the risk-based approach be further clarified/documented to avoid overlap/potential gaps between EMA and MAH follow-up requirements Required outcome: Follow-up - Process clarity/compliance
15	Lines 209 -212	It is not clear that the MAHs will be made aware of Agency follow up for reports not meeting reporting criteria. Also will the “tracking table with the attempt to obtain FU information” be available to MAH?	Proposed change: Add to section 4.1.2: “Where follow up is pursued for the serious cases not meeting minimum reporting criteria, this will be published along with the valid ICSRs listings and updated if/when follow up is received.” Required outcome:

Stake holder no.	General comment/ Line number	Stakeholder comments	Proposed changes by Stakeholder, if any
			Follow-up - Process clarity
15	Line 216	Re: **"**Where a MAH obtains additional follow-up information outside the follow-up process operated by the Agency, the MAH should send a follow-up case with the new information to EudraVigilance." This recognises the need for efficient duplicate checking by both the Service provider and the MAH (upon download) for ICSRs already entered pre-publication, and that the MAH may already be seeking or have additional information.	Proposed change: In case of MAHs identifying duplicates and having follow-up in process or where additional information needed, will the Agency consider a process for the literature vendor to consolidate data and/or additional questions from MAH - follow-up accordingly to the author? Please define the process if a literature report is not captured by EMA provider and is later identified by MAH? Required outcome: Duplication/Follow-up: Process clarity/compliance
15	Lines 238-239	The electronic format should enable the MAH to import the ICSR directly into the PV DB of MAH.	Proposed change: The ICSRs entered in EudraVigilance as a result of the scientific and medical literature screening activities are published daily in ICH E2B xml format for download by MAHs. Required outcome: Technical - Process clarity
15	Lines 238-246	With the product-specific expertise held by the MAH, a non-MAH literature group may not recognise particular events as medically significant for a specific product, thereby classifying a serious adverse event	Proposed change: We would propose that

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		incorrectly as non-serious.	there is a mechanism for MAH input and comment on classifications Required outcome: Assessment - Process clarity/compliance
15	Lines 241-244	“A listing is provided to MAHs for ease of identification of applicable ICSRs at the EudraVigilance restricted website.” MAH will need to perform reconciliation between the ICSR posted on the EudraVigilance restricted website and their global safety database, accordingly; Is the listing provided to MAH updated daily? Will the updates from this listing be highlighted in order to facilitate the tracking of newly added/corrected information? Will the title of the article, author's names or Journal title and the reported ADR(s) be provided to assist with a duplicate check when performing reconciliation?	Required outcome: Lists/Reconciliation - Process clarity/compliance
15	Lines 248-249	Given the impact on the MAH PV System and QMS for the Products authorized in the EEA, will the Agency regularly release data from the quality management practices, including any observations/area's for improvement, root cause analysis, corrective and preventative actions? How should MAHs organize the documentation in their PSMF?	Required outcome: QMS - Process clarity/ Transparency
15	Lines 259-260	Would it be possible to specify the types of enquiries which can be sent to the proposed service desk (i.e. case processing issues, questions related to assessment of the cases, technical issues or performance issues).	Required outcome: Service Desk - Process clarity
15	Line 265	Further details for the pilot are required including who is involved and when it will happen.	Required outcome: Pilot - Process clarity
15	Lines 247-266	What if quality requirements are not met? Will process transition to another provider or revert back to MAH?	Required outcome: QMS - Process clarity
16	General comment	AESGP appreciates being consulted on this draft detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency. We also appreciate that our key principles have been reflected in the guide. However the issue of liability is not addressed i.e. it should be clarified (either in the guide or on the introduction thereon on the website) that the MAH is not liable for the actions carried by the EMA in terms of literature screening and processing of outputs. In other words, the MAH can fully rely on the EMA literature monitoring work and does not have to do it by itself to avoid duplication which would defeat the benefit of the system. As long as EMA’s responsibilities in terms of literature monitoring are clearly defined and delimitated, the MAH could refer to them for e.g., during a pharmacovigilance inspection from an authority within EU. It would be very helpful if the date at which the service will start being operation could be known in advance so that MAHs could better plan for the transition internally. More clarity should be also provided on the quality standards	

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		of case entry / data capture. At present the draft guidance only refers to GVP VI and IR 520/2012 standards (194 section 4.1.1). However, literature articles have their own peculiarities. Therefore we consider it worthwhile to specify that: - the intention of the author should primarily be followed with regards to both the adverse reaction terms to be captured in the database and also with regards to a suspected causal relationship with the products in question. Unless this happens, literature articles may trigger the processing of many incidental events, i.e. such occurrences that took place whilst a patient was taking the product (e.g as reported in the patient's history at a point in time that is different from the date the episode occurred which the authors publish about). Also many events may be captured for which the author did not suspect / mention any causal relationship with the product in question in their article; - no adverse events will be created in the database for articles providing aggregate data.	
16	Lines 89-93	The criteria for including a substance or a group of substances should be made known.	
16	Lines 91-93	Industry consultation on the list would be optimum; alternatively the provision of input from companies on substances on the list should be made possible.	
16	Lines 115	'Non-indexed journals are excluded from the Agency's monitoring activities and remain under the responsibility of the MAHs'. Comment: This will create additional work for the MAH and conflicts with the Key Principle of 'Avoiding partial service that would necessitate duplicative efforts by MAHs' (Line 71).	
16	Lines 117-120	The provision of input by industry on the literature being monitored should be possible.	
16	Lines 133/240	The issue of Bank Holidays should be addressed as well.	
16	Lines 145-149	MAHs should be informed when search constructions are updated and maintained to improve search precision.	
16	Line 162	'A flag to highlight literature that refers to situations of lack of therapeutic efficacy, pregnancy, off-label use' Comment: What is the rationale behind flagging this literature entailing various special situations (which may or may not involve any adverse reactions) over literature containing adverse reactions? The flagged articles may or may not be less relevant than such articles reporting actual reactions.	
16	Line 192	Individual cases related to purely non-serious adverse reactions, with a primary-source country outside the EEA are excluded from EudraVigilance'. Comment: This will create additional work for MAHs responsible for submitting non-serious cases outside of the EU to set up their respective processes and also ensure to enter the respective cases into their databases.	
16	Line 206	'One attempt to follow-up with the primary author is made for serious adverse reactions'. Comments: One follow-up attempt for serious and no action for non-serious cases appears to be below the usual industry's operating standards. In addition, the GVP VI requests to conduct appropriate follow up attempts. This would have a practical impact and a risk of duplication of effort and ultimately cases (see comment on line 216-217 below).	

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16	Line 216 – 217	'Where a MAH obtains additional new information outside the follow-up process operated by the Agency, the MAH should send a follow-up case with the new information to EudraVigilance'. Comment: This is likely to result in duplication of effort as several MAHs will follow-up cases to different degrees and will submit different versions of follow-up for the same case to the Agency therefore going against the key principle of 'Avoiding partial service that would necessitate duplicative efforts by MAHs' and avoiding case duplication.	
16	Line 232	Copies of articles should also be accessible to MAHs.	
16	Lines 238-240	It is not clear which "electronic format" to be downloaded is meant. The case should be available as CIOMS form and as xml-file - as it is the case on the website of the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) - in order it can be directly uploaded into the data base. Otherwise, it would have to be typed manually.	Change therefore lines 238-240 into "The ICSRs entered […] are published daily in electronic format (CIOMS I form and xml-file) for download by MAHs."
16	Lines 238-240	It would be good if MAHs could be notified of any new relevant ICSRs entered into Eudravigilance.	
16	Line 242	Who will have access to the EudraVigilance restricted website? Only QPPVs and their deputies?	
16	Lines 247-266	At least at the beginning, regular platform with the industry, the EMA and the contractor should be organised to discuss potential issues, remedial solutions, etc. A mail contact should be made available to send issues or questions concerning literature monitoring when the service has started.	