29 July 2014

Submission of comments on Draft detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency (EMA/161530/2014)

Comments from:

| EFPIA |
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| EFPIA – Sini Eskola (sini.eskola@efpia.eu) |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements:* <http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid> *and* <http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf>*).*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation:* <http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf>)*.*

1. General comments

| Stakeholder  | General comment | Required Outcome |
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|  | **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’.**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
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

**Missing Information:**1. **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)
2. **Suspected transmission of an infectious agent** – such ICSRs required per GVP but not mentioned in current draft
3. **Screening for articles meeting ‘Special Situation’ criteria** – or as per GVP MAH will still need to screen same product/literature combinations to identify these
4. **Reference to excluding articles by agencies and meta-analysis -** i.e. exclude ‘already reported’ and ‘republished data’
5. **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
6. **Process defining how/when concomitant medications within an article will be handled** - i.e. would they ever be ‘upgraded’ to suspect?
7. **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)
8. **The actual implementation date is unclear** - clarity would aid MAH preparation
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1. Specific comments on text

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| Line number(s) of the relevant text*(e.g. Lines 20-23)* | Stakeholder  | Comment and rationale; proposed changes*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | TOPIC/Required Outcome |

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| 82-9394-120 | EFPIA | **Comment:** 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  | Literature:MAHs will have the opportunity to comment on the list of active substances and literature that the agency is monitoring, if applicable. |
| 94-120 | EFPIA | **Comments:** 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  | Special Situations:Avoid Duplication of effort / Compliance  |
| 100 | EFPIA | **Comment:** 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. | Aggregate Data:We recommend to provide a position and to update these documents in order to ensure consistency in the data entry process |
| 100-109 | EFPIA | **Comment:** Will the agency perform duplicate checks against EV to ensure case not previously reported by MAH during 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? **Proposed change:** Perhaps the Agency could suggest a mechanism or processes to help MAHs with duplicate identification. | Duplicate Checks: Ensure clarity, without which we perceive a risk of creating duplicate ICSRs with different WWCIDs. |
| 100-109 | EFPIA | **Comment:** 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? | Follow-up: Process clarity |
| 100-109 | EFPIA | **Comment:** 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 metanalysis will be excluded. | Exclusions:Process clarity |
| Line 101 | EFPIA | **Comment:** 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 | Exclusions: Avoid duplication of effort |
| Line 103-106 | EFPIA | **Comment:** 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) | Alignment:Harmonisation between sections 2.2. and 3.1 |
| Line 103 | EFPIA | **Comment:** 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 which are based on an analysis from a competent authority database within the EU. | Exclusions:Process clarity |
| 107-109 (and 129-131) | EFPIA | **Comment:** 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. | Suspected Transmission:Avoid duplication of effort |
| 111 | EFPIA | **Comment:** 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” | Literature Scope:Process clarity |
| 115 | EFPIA | 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. | Local Literature:Process clarity |
| 119 | EFPIA | **Comment:** 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 | Search Criteria:Transparency / Compliance |
| 126 | EFPIA | **Comment:**  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?  | Assessment:Process clarity |
| 130 | EFPIA | **Comment:** 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…” | Off-label Use:Process clarity / Compliance |
| 132 | EFPIA | **Comment:**  Re“*The screening includes all suspected serious and non-serious adverse reactions...”, w*ill the EMA explicitly search for a specific causality in each article? | Causality:Process clarity |
| 137-138 | EFPIA | **Comment:** To comply with the worldwide regulations it is required to take all international trade names into account.**Proposed change (if any):** 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.  | Search Criteria:Process clarity / Compliance |
| 140 | EFPIA | **Comment:** 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. | Search Criteria:Process clarity  |
| 141 | EFPIA | **Comment:** 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 | Search Criteria:Process clarity  |
| 141-143 | EFPIA | **Comments:** 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?**Proposed change (if any):** Please provide clarification | Assessment:Process clarity / Compliance |
| 144 | EFPIA | **Comment:** Will the MAH have access to the audit report? | Access: Process clarity  |
| 145-9 | EFPIA | **Comment:** 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 indexing as well as to the substance groups as referred to in chapter 2.1. . Updates are announced in due time by the Agency. | Search Criteria:Process clarity  |
| 158-161 | EFPIA | **Comment:** 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? | Translation:Process clarity  |
| 166-167 | EFPIA | **Comment:** 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 basisand will include the above referenced data to allow the MAHs to identify if any ICSRs for their products have been identified from the search”.  | Published Lists:Process clarity |

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| 166-167 | EFPIA | **Comment:** 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 applicablePlease confirm the registration process to have the ability to download ICSRs from Eudravigilance | Access:Process clarity for access to the restricted website.  |
| 168 | EFPIA | **Comment:** Will *“records of literature searches”* be accessible to MAH? | Access:Process clarity  |
| 177-246 | EFPIA | 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? | Data Privacy:Process clarity  |
| 182-185 | EFPIA | **Comment:** 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.” | Clock Start:Process clarity / Compliance |
| 190-192 | EFPIA | **Comment:** 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 | Non-Serious:Process clarity / Compliance |
| 192 | EFPIA | **Comment:** 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.” | Outside EEA:Process clarity |
| 194 | EFPIA | **Comment:** 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 | Incidental Events:Process clarity |
| 195 | EFPIA | **Comment:** 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? | Exclusions:Avoid duplication of effort / Compliance |
| 203 and 216 | EFPIA | **Comment:** 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 | Follow-up:Process clarity / Compliance |
| Line 209 -212 | EFPIA | **Comment:** 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.” | Follow-up:Process clarity  |
| 216 | EFPIA | **Comment:** 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? | Duplication / Follow-up:Process clarity / Compliance |
| 238-239 | EFPIA | **Comment:** 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.  | Technical:Process clarity |
| 238-246 | EFPIA | **Comment:** 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 incorrectly as non-serious.**Proposed change:** We would propose that there is a mechanism for MAH input and comment on classifications  | Assessment:Process clarity / Compliance |
| 241-244 | EFPIA | “A listing is provided to MAHs for ease of identification of applicable ICSRs at the EudraVigilance restricted website.”**Comment:** 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? | Lists / Reconciliation:Process clarity / Compliance |
| 248-249 | EFPIA | **Comment:** 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?  | QMS:Process clarity / Transparency  |
| 259-260 | EFPIA | **Comment:** 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). | Service Desk:Process clarity |
| 265 | EFPIA | **Comment:** Further details for the pilot are required including who is involved and when it will happen. | Pilot:Process clarity  |
| 247-266 | EFPIA | **Comment:** What if quality requirements are not met? Will process transition to another provider or revert back to MAH?  | QMS:Process clarity  |