14 October 2016

Submission of comments on *Guideline on good pharmacovigilance practices (GVP) – Module VI – Management and reporting of adverse reactions to medicinal products (Rev 2)* – EMA/873138/2011

Comments from:

| Name of organisation or individual |
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*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number  *(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)  *(To be completed by the Agency)* |
| --- | --- | --- |
|  | EFPIA welcomes the opportunity to provide comments on revision 2 of GVP Module VI. The revision mainly focuses on implementation of the ICH E2B (R3) format for transmission of Individual Case Safety Reports (ICSRs). It is anticipated that the E2B(R3) format for ICSRs will gradually transition from the ICH E2B(R2) approximately six months after the functionalities of the EudraVigilance database specified in Art. 24(2) of Reg. (EC) No 726/2004 are established.  Other modifications that relate to ICSR management are also been proposed in this draft revision of GVP Module VI.  Many of the technical and process details requiresupport from vendors to implement and, of course, there is residual uncertainty regarding timing. These present formidable challenges.  While, overall, EFPIA agrees that updates to GVP Module VI are needed, there are a number of general and specific concerns that EFPIA believes merit further consideration before the proposed changes are finalised. |  |
|  | **Additional Complexity & Bureaucracy**  The draft revision of GVP VI indicates that many of the proposed requirements and obligations have become very detailed and unnecessarily specific in their nature. EFPIA would like to challenge the Agency for the need to be so specific on the processes and procedures of collecting initial and follow-up for spontaneous ICSRs. It is a desire of EFPIA companies to maintain some flexibility to develop their processes that drive compliance. Pharmacovigilance is rapidly evolving science and for instance the data sources with potentially important safety information are emerging. In this regard, EFPIA proposes a forum that would support a dialogue amongst stakeholders that would aim to streamline the management of spontaneous of ICSRs. In addition to MAHs and CAs, the scope of such a discussion would encompass engagement MAHs and CAs . This also supports the principle of proportionality: we will probably increase the quality of the case reports to some level, but the effort needed to get there is not in proportion.  There are also a number of updates within the revised Module, which we understand will increase the complexity and burden for industry, regulators, prescribers and patients. Most important ones are the new validation rules and the newly proposed follow-up process. These and other examples of increased complexibility are described later in our response document. |  |
|  | **Terminology and Consistency**  EFPIA welcomes the proposal from the Agency to change the terminology from reporting to submitting. It brings much more clarity around the concepts of receipt from reporter versus expedited submission to the Agency. However, we have noted that there is an inconsistent use of reporting vs submitted throughout the revised Module and Agency could consider document all the instances where this needs to be changed under the revision notes. Some examples of inconsistency would appear to be in lines 436, 443, 573, 981 and therefore we would suggest they are changed to the word “submitted” or “submit” throughout the entire document. The same holds true for deleting references to the interim arrangements (e.g. line 1728, 2215 and 2249).  We have also noted that it would be needed to ensure consistency in approach to cross-referencing within the document as well as to other guidelines. An example would be in line 417 where a cross-reference could be added to GVP Module IX acknowledging that searching literature for signals is covered there and is not covered in GVP Module VI. Another example is related to the removal of the examples of the Emerging Safety Issues; while they have been deleted with a cross-reference to Module IX, there is little additional information in Module IX to help the MAH understand the threshold for reporting events as Emerging Safety Issues. Re-instating or redrafting examples in Module IX would be beneficial to MAHs to help reduce inappropriate and over-burdensome reporting via this route.  In addition, the current version of the guideline leads to more divergence between the European standards and the other global standards. EFPIA wants to particularly point out two examples: the application of the Null Flavours, where the EU has added its use for some specific situations, and the new validation criteria, where it is clear that certain territories still accept the existence of “a patient” as sufficient to have a valid case. |  |
|  | **Structure and Content of the Guideline.**  While reviewing the guideline, EFPIA members find it a complex document where process, guidance, technical requirements and business rules are interlinked. It has also been noted that the implementation guide, which in the end should be a rather technical document, does contain a lot of process related content. We understand the rationale to keep some sanity in the number of documents; however, EFPIA would like to urge the Agency to reconsider the content with a clear idea of the final objective of it.  With the increased number of supplemental documents, this revised Module has become more difficult to interpret as a stand-alone piece of text. The annexes themselves are very duplicative and it appears that these could be streamlined. An example of this is the follow up process for MAHs and for Competent Authorities which could be merged, as they are the same. Another example would be to either display the process flow chart or the step action tables for each topic as they describe the same process.  There is an increased amount of technical specifications within this document which is a repeat of the ICH documents. There is a concern that some companies may use this document instead of the ICH E2B documents. |  |
|  | **Related to the validation of ICSRs based on patients and reporters identifiability**  The criteria for a valid patient and reporter are now very stringent which EFPIA thinks will lead to an increased number of non-valid cases. There is also concern that this does not align with the valid reporter criteria in other territories which leads to increased challenges for MAHs to comply with differing global requirements. For example, per the US FDA, a professional identifier alone is sufficient for a reporter to be considered valid. Health Canada considers a patient valid if the MAH knows that “a patient” exists.  This change would have a significant technical impact on the case validity definition for MAH to ensure an appropriate expedited reporting in Eudravigilance (EU) versus reporting HA outside EU. This has also the potential to greatly complicate other activities relating to global activities such as PSUR analysis and producing outputs from the global safety database , as cases will simultaneously be valid for reporting in some places and invalid in others.  Prior implementation of these changes, EFPIA recommendation is to further discuss within ICH to assess these new criteria on a worldwide basis. |  |
|  | **Related to following-up of case reports**  In the follow-up process described in line 1039 and in Appendix 1.3, the follow-up of ICSRs by competent authorities with involvement of MAHs could lead to unnecessarily bureaucratic tasks. EFPIA would highly recommend that the requirements for MAHs to conduct follow-up should only be in rare circumstances with very specific questions where a competent authority would need to request follow-up from an MAH.  Additionally, while follow-up may not be necessary for validation of the report, this does not necessarily mean follow-up to clarify ambiguities or solicit additional information is inappropriate, even though the initial version of the case will qualify for submission anyway. Reference is made here to line 2266 (Item 9 in the table).  In the same table from line 2266, items 8.1 and 14.1 describe an expectation that MAHs will update their database if attempts to procure follow-up are unsuccessful, simply to record this fact. EFPIA wants to challenge this requirement as in many companies it is a standard practice to document unsuccessful follow-up attempts at the local level, as a function of Medical Information or the local operating company, rather than in the centralised PV database. Routinely duplicating this into the safety database seems to add little obvious benefit, particularly as PV database cases are never considered ‘closed’. Furthermore, the table does not provide guidance regarding how much time should be allowed to elapse before absence of a response should be taken to indicate an unsuccessful follow-up attempt. This may vary from a MAH to another. |  |
|  | **Interventional Clinical Trial provisions**  We believe the revised version in lines 910/920 and lines 2060-2064 is now more misleading. EFPIA would recommend making sure the definitions or references in this document are consistent with the concepts presented in the Clinical Trial Regulation. CT3 and Article 46 of [Clinical Trials Regulation (CTR) EU N°536/2014](http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf) clearly stipulated that the reporting of NIMP should follow the Post Marketing reporting.  Furthermore more, even if the CTR is not yet effective, NIMP will be replaced by Auxiliary Medicinal Product (AMP). This terminology should also be used in the revised Module. |  |
|  | **Missed Opportunities**  In addition, EFPIA would like to express our disappointment that a number of topics were not covered in this revision. Although it is clearly stated that the public consultation is restricted to the revised texts or deleted texts highlighted in “track changes” mode, we want also to highlight a number of topics that have not been addressed in this revision. For example, EFPIA submitted a position paper on Patient Support Programmes in October 2013 which included the wish for a major revision. In addition, it would have been now an opportunity to revise this module taking into account the off-label use reflection paper which included a number of sensible recommendations. |  |
|  | **Effective Date**  EFPIA would appreciate if EMA can release a second request for comments for the next revision (Rev 3) which in our opinion is duly justified as the effectiveness of this Module is planned only once Eudravigilance (EV) is fully functional. This would give us an opportunity to comment other aspects, not covered in this revision. |  |

1. Specific comments on text

| Line number(s) of the relevant text  *(e.g. Lines 20-23)* | Stakeholder number  *(To be completed by the Agency)* | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome  *(To be completed by the Agency)* |
| --- | --- | --- | --- |
| 231 |  | **Comment:** As with the new legislation reports from healthcare professionals and consumers are treated equally it should be added at the end of the paragraph that a healthcare professional’s causality assessment cannot overrule a consumer’s causality assessment. E.g. if there are two sources and a consumer states that the event is related and a healthcare professional states that the same event is unrelated, the overall causality is related. Addition of the following sentences is proposed:  **Proposed change (**to add a sentence):  In cases of two report sources - healthcare professional and consumer - the healthcare professional’s causality assessment cannot overrule the consumer’s causality assessment. If there are two different causality assessments (related and unrelated), causality for the event is related. |  |
| 239-240  242-243 |  | **Comment:** In the definition of off-label use and misuse it refers to use outside of the terms of the marketing authorization – Clarification onwhich marketing authorization should be used for the determination of off-label use i.e. is it the MA in the country of origin of the report, or the EU MA would be beneficial. For simplicity EFPIA would hope that this is the MA in the country of the origin of the report .  **Proposed Change:**  “This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation **in that country**.” |  |
| 241 – 243 |  | **Comment:** This definition is not harmonized with the one in the definition published in MedDRA® TERM SELECTION: POINTS TO CONSIDER - ICH-Endorsed Guide for MedDRA Users, Release 4.12, 1 September 2016, which defines misuse as the following:  “Misuse  For the purposes of term selection and analysis of MedDRA-coded data, misuse is the intentional use for a therapeutic purpose by a patient or consumer of a product – over-the-counter or prescription – other than as prescribed or not in accordance with the authorised product information.  **Proposed Change:**  To align Misuse definition to with the MedDRA definition*.* |  |
| 289-297 |  | **Comment:** This is new text regarding the applicable legislation to follow for medical device type products. It is clear that the applicable legislation to be followed is dependent on how the product was registered i.e. either as a medicinal product or as a medical device. The paragraph then goes on to state that if the action of a medicinal product component is ancillary to that of the device that the device legislation should be followed. We assume therefore that all such products would in fact be registered as medical devices, and if not that this last sentence would conflict with the earlier instructions. EFPIA propose therefore to remove the wording regarding the action of a medicinal product being ancillary to the device  **Proposed change** (replace section line 289-297 by the below one):  “For devices containing active substances, whether they are authorised in the EU as medicinal products or CE marked as medical devices determines which procedure should be followed for the safety reporting of suspected adverse reactions and/or incidents. In this aspect, registered medicinal products follow the requirements for pharmacovigilance provided in Directive 2001/83/EC and Regulation (EC) No 726/2004, whereas marked medical devices follow the requirements for medical device vigilance in accordance with Directive 90/385/EEC and Directive 93/42/EEC. ” |  |
| 310-313 |  | **Comment:**  EFPIA seeks clarification on country of occurrence vs. country of reporter and how this impacts the HA to which the case should be reported. The text here seems to be contradictory as it refers to the person who first reported the facts (who may be in a different country to the country of occurrence of the AE), whereas if there are multiple reporters it refers to the country of the source where the AE occurred.  Clarification on whether the reporting of ICSRs to HAs should always be based on the country of occurrence of the AE, or the country of occurrence of the primary source (which could be different).  If reporting should be based on country of occurrence you could have a situation where the product does not have an MA in the country of occurrence and therefore would not be reported. EFPIA would propose that reporting should be based on the country where the drug was obtained. In the frame of ICH E2B (R3) implementation, the recommendation would be to ensure a consistency approach on this statement is done.  **Proposed change** (if any):  Replace the “country where the case occurred” by the “reporter’s country” |  |
| 314-315 |  | **Comment**:  The wording suggests that subsequent confirmation of occurrence of the event by a healthcare professional or a description of the event in medical documentation would imply a causal association with the medicinal product, regardless of whether or not an assessment of causality is provided.  In addition, using the documents cited in the draft Module, it is not clear if such reports should be submitted whether or not the HCP provides a statement of a suspected causal relationship.  As per ICH–M2 EWG – *Electronic Transmission of Individual Case Safety Reports Message Specification* (listed in section B.8 Reporting Modalities), the concept is linked just to the occurrenceand not necessary linked to the causal relationship that may be provided by the HCP. See ICH-M2 text below:  *“If an event is reported by a non-healthcare professional (e.g. lawyers, consumers), this data element indicates whether the occurrence of the event was subsequently confirmed by a healthcare professional. If the healthcare professional also provides an assessment of causality (related or not to the suspect drug), that should be recorded in G.k.9.”*  Whereas per *Note for guidance - EudraVigilance Human - Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (EMA/H/20665/04/Final Rev. 2) (also referred to as EudraVigilance Business Rules),* section *10, “Qualification and medically confirm”, (*cited *in section* C.6.1. of Module VI: *Applicable guidelines, definitions, international formats, standards and terminologies),* a case is considered medically confirmed if the HCP suspects a causal relationship.  The intended meaning of “medically confirmed” for reports originally received from non-HCPs is not clear. Likewise, it is not clear whether a causal relationship that may be provided by the HCP should be considered the driver for classifying the case as medically confirmed or not medically confirmed.  **Proposed changes:**  Revise lines 321-322 as follows, “**~~Similarly a~~ A** report may **also** be submitted by a medically qualified patient, friend, relative or carer of patient. In these situations, the reported information is considered medically confirmed.”  Revise lines 325-329 as follows, “In the same way, where one or more suspected adverse reactions initially reported by a consumer is subsequently confirmed by a healthcare professional or contains medical documentation that supports the occurrence of a suspected adverse reaction, the case should be considered medically confirmed. It should be updated at case level in line with ICH-E2B(R2), or at adverse reaction level in accordance with ICH-E2B(R3) for each subsequently medically confirmed suspected adverse reaction. **A specific statement of suspected causality is not required in the medical documentation, either at the case level or at the level of each suspected adverse reaction that is considered medically confirmed**.” |  |
| 408-409 and 413-416 |  | **Comment:** As per new guidance, a notification spontaneously reported directly by patient/HCP and then also collected through an organised collection scheme such as PSP/ non Interventional Studies, should now be considered as unsolicited. EFPIArecommends considering such situation as a solicited report as the patient is included in an organised collection scheme.  **Proposed change** (if any):  Delete sentence in this section VI B.1.2.  Add this situation in the solicited reports section VI B.1.2. |  |
| 413-415 |  | **Comment:** Unclear whether this sentence should be a bullet point (as per 399-412) so is stating that where these reports are collected, they should be reported spontaneously, or whether it is stating that if these ICSRs are collected by (or reported to) the company, they should not be reported to the EMA.  **Proposed change:**  Add bullet point:   * Reports of suspected adverse reactions originating from compassionate use or named patient use conducted in a country where the active collection of adverse events occurring in these programmes is not required (see VI.C.1.2.2. and VI.C.6.2.3.7. subsection 2). |  |
| 420-425 |  | **Comment:**  “Marketing authorisation holders are therefore expected to maintain awareness of possible publications through a systematic literature review of widely used reference databases (e.g. Medline, Excerpta Medica or Embase) no less frequently than once a week.”  **Proposed change:**  It would be useful to amend the text to add a caveat about the change to the MAH requirements, when global literatures searches of the databases mentioned in the text are being conducted by the EMA. |  |
| 438-439 |  | **Comment:** EFPIA would recommend adding a statement to mention that this guidance applies only when the case is firstly received as a publication.  **Proposed change** (if any):  Relevant medical information should be provided, the first publication author(s) should be considered as the primary source(s)**. If the case was initially received as a publication, it should also considered as** the primary source for regulatory purposes in line with ICH-E2B(R3) (see VI.A.2.3.). |  |
| 469/471 |  | **Comment:** “In absence of any reporter identifier, the country where the information was received, or where the review took place, should be used as identifier and as the primary source country”.  This reporter identifier information is relevant not only for information coming from internet or digital media, EFPIA would recommend adding this statement in section VI. B.2 validation of reports  **Proposed change** (if any): Move sentence after line 519 |  |
|  |  | **Comment:** To add the following patient qualifiers corresponding to patient E2B R3 fields that may also be considered as qualifiers.  **Proposed change** (if any):  - To include qualifiers such eg. weight, height, medical or product history, cause of death, information on parent (for fetus/child case)  - to add also “screen name” in the footnote 15 |  |
| 498-515 / VI.App.8 examples 3 and 14 |  | **Comment:** The handling of cases whether or not valid should be furthermore clarified when there is multiple patients. Some Members States have requested to split cases if several patients are mentioned in the report, even in absence of patient qualifier(s).  Proposed change (if any):  **Add a sentence:** When there is a notification with multiple patients, separate report should be created if lead to valid report. |  |
| 500-501 |  | **Comment**: Is this to be a new business rule? ie. reporter MUST have at least one parameter of either name, address or phone number supplied  Proposed change (if any): add a reference (to this sentence) to the Business rule, if this is indeed the intent. |  |
| 500-501 |  | **Comment:** If the requirement to supply either name, address or phone number supplied for a reporter is confirmed as a new business rule, can it be made clear whether the business rule would apply to ICSRs sent in R2 format from Nov. 2017 ?  **Proposed change** (if any): Add reference to business rule with this clarification |  |
| 512-515 |  | **Comment:**  The text states: “*Furthermore, as specified in ICH-E2D, a report referring to a definite number of patients should not be regarded as valid until the patients can be characterised by one of the aforementioned qualifying descriptors. For example, “Two patients experienced nausea with drug X …” should not be considered valid without further information;”*  Same comment as per lines 498-502.  EFPIA is wondering if the intention of this section is to limit validity criteria for reporting to only those cases where specific patient’s qualifying criteria are identified. This would exclude those scenarios (e.g., lines 514-515, “Two patients experienced nausea…”) where instead there could be a clear first-hand knowledge by the reporter (see also example referenced below). This would also be inconsistent with consensus recommendations in the CIOMS V report. Is the intent to limit where the reporter is clearly not identifiable? If so, this should be clarified as the currently proposed language does not convey this.  Appendix 8, example 6:  *Dr. Bones reports via e-mail that her patient developed a melanoma after taking drug X. Dr. Bone’s address and phone number are not available, but she does respond by e-mail*.  It is not clear to us why this case is considered invalid. The reporter is contactable via email and it is evident that the physician is referring to one of her patients (although the patient is not identified by name, age, initial or gender, etc), but still linked to a specific event and product. See reference to email in footnote 15, line 527.  Proposed changes: Modify lines 510-512 as follows, “An ICSR should not be considered valid for reporting unless information is available for at least one of **~~the~~ these** patient qualifying descriptors **or the reporter has first-hand knowledge that the patient exists.**”  Modify lines 514-515, per ICH E2D (p 6), as follows, “For example, “Two patients experienced nausea with drug X …” **~~should not be considered valid without further information~~ should be followed up for qualifying descriptors for patient identifiability. *However, regulatory reporting would be appropriate as long as there is first-hand knowledge by the reporter***;  Modify lines 2714-2717, Appendix 8, example 6, third column, “**~~Non-valid~~ Valid** case. Identifiable reporter and qualification. No patient’s qualifying descriptor available**, but identifiable reporter has first-hand knowledge of the patient and the suspected adverse reaction**. Report should be followed up.” |  |
| 520-523 |  | **Comment:** For any organised collection scheme, EFPIA would like that a clear statement is mentioned when no explicit causal relationship was received from the reporter despite FU attempts request by MAH.  **Proposed change** (if any):  Despite FU attempts request by MAH, if no causal relationship was received from the reporter, in this instance, the MAH causal relationship prevails. |  |
| 533 |  | **Comment:** As the new processes will be submission to EudraVigilance only., please rephrase.  **Proposed change** (if any):  Add: “…and valid ICSR should be submitted to Eudravigilance.”  Delete “to competent authorities” |  |
| 551-557 |  | **Comment:**  This paragraph appears to contradict **ICH–M2 EWG** – *Electronic Transmission of Individual Case Safety Reports Message Specification, which states the following:*  *“If an event is reported by a non-healthcare professional (e.g. lawyers, consumers), this data element indicates whether the occurrence of the event was subsequently confirmed by a healthcare professional. If the healthcare professional also provides an assessment of causality (related or not to the suspect drug), that should be recorded in G.k.9****.”***  If an initial non-HCP reporter implies a causal relationship with the drug and then a follow-up received from an HCP denies causality, then the HCP causality cannot be entered in G.k.9 for the reporter.  **Proposed change:**  Modify lines 551-557 as follows, “A valid case of suspected adverse reaction initially reported by a consumer cannot be downgraded to a report of non-related adverse event if the contacted healthcare professional (nominated by the consumer for follow-up information) subsequently disagrees with the consumer’s suspicion  (see VI.A.2.1.1.). In this situation, the opinions of both the consumer and the healthcare professional should be included in the ICSR. Guidance on the reporting of the medical confirmation of a case, provided in VI. A.2.3. should be followed. **In instances when a healthcare professional provides follow-up with causality that contradicts information in an initial report from a consumer, this should be described in the case narrative and not in G.k.9., per ICH M-2**.” |  |
| Line 575 |  | **Comment:** The sentence “All possible efforts should be made to follow-up…” could lead to exaggerated interpretations/expectations on how these follow-ups should be handled.  **Proposed change** (if any): “**Reasonable** efforts should be made to follow-up on…” |  |
| 589-592 |  | **Comment:**  EFPIA is wondering if there is currently an expectation that all consumer reports will be followed up (where permission and contact details are provided by the consumer), in order to obtain HCP confirmation of the events or is the expectation that the HCP will only be contacted if there is missing information in the consumer report? It would be useful to clarify the current expectation in the text.  **Proposed change:**  “When information is received directly from a consumer suggesting that an adverse reaction may have occurred, **and** if the information is incomplete, attempts should be made to obtain follow-up with the consumer to collect further information and to obtain consent to contact a nominated healthcare professional to obtain further follow-up information.” |  |
| 602-605 |  | **Comment:** This is not specific to cases related to medication errors that result in harm.  **Proposed change** (if any):  For individual cases, ~~related to medication errors that result in harm~~, it may not always be possible to perform follow-up activities taking into account that the primary source information may have been anonymised in accordance with local legal requirements or due to provisions that allow for anonymous reporting. |  |
| Lines 629-630 |  | **Comment:** Requirement to include original verbatim in local language AND an English translation is covered in R3. Not so in structured R2 fields.  **Proposed change** (if any): Revert to previous requirement of local language OR an English translation. Alternatively clarify the difference of R2 versus R3. |  |
| 643-646 |  | **Comment:**  Text in line 643 -644 states that “appropriate use of terminologies” should be monitored by “quality assurance auditing”.  The following sentence in line 645-646 refers to verification by “quality control procedures” and does not include verification of “appropriate use of terminologies”.  What is the difference between “quality assurance auditing” and “quality control procedures”? Why is “appropriate use of terminologies” not included in “quality control procedures”?  Please provide clarification on which terminologies.  **Proposed change** (if any):  Remove text in line 643-644 and add “appropriate use of terminologies” in line 645:  ~~Correct data entry, including the appropriate use of terminologies, should be monitored by quality assurance auditing, either systematically or by regular random evaluation.~~  Conformity of stored data, including the appropriate use of **pharmacovigilance and MedDRA** terminologies with initial and follow-up reports should be verified by quality control procedures, which permit for the validation against the original data or images thereof. |  |
| 656-657 |  | **Comment:** Please provide clarification on which terminologies? the rest of the sentence is about legislation and guidelines, but no mention of 'terminologies'  **Proposed change:** Data entry staff should be instructed in the use of the **pharmacovigilance and MedDRA** terminologies, and their proficiency confirmed. |  |
| Line 740 |  | **Comment:** In line 740 it is stated that reports of lack of therapeutic effect without associated adverse reaction should not be submitted as ICSRs presumably to the competent authorities. It is not clear however whether these reports should be collected in the company’s database or not. Clarification is proposed as follows:  **Proposed change** (if any): They should **be collected however** not normally be submitted as ICSRs if there is no associated… |  |
| 747-750 |  | **Comment:** Make it clear that this sentence is referring to post authorisation efficacy studies (PAES): "The requirement to submit these reports of lack of efficacy does not apply when the notification occurred in the frame of a non-interventional efficacy study."  **Proposed change:** “The requirement to submit these reports of lack of efficacy does not apply when the notification occurred in the frame of a non-interventional **post authorisation efficacy** study.” |  |
| 988 |  | **Comment:** Despite rewording in this version, still seems to have the potential for confusion between situations in which specific adverse events are exempted per-protocol and in which no adverse events are solicited per-protocol.  **Proposed change** (if any): Rephrase this line as “For protocols which do not mandate the systematic collection of adverse events [...]” |  |
| 1002 |  | **Comment:** Please align wording / clarify requirements between Modules VI & VIII to avoid confusion.  **Proposed change**: "For post **authorisation safety studies (PASS) based on secondary use of data, the collection of all adverse events is required, however** the reporting of suspected adverse reactions in the form of ICSRs is not required (**for more information refer to Module VIII**)" |  |
| 1033-1044 |  | **Comment:** description of the process of follow-up by combination of MAH and CA needs to be tightened. A CA would only follow up on cases they receive directly.  **Proposed change:** Member States shall involve patients and healthcare professionals, as appropriate, in the follow-up of any reports they receive **directly** in order to comply with Article 102(c) and (e) [DIR Art 107a(1)]. |  |
| 1157 |  | **Comment:** With simplified reporting, valid ICSRs would only be submitted to EudraVigilance and not to the individual competent authorities.  **Proposed change** (if any):  ..which should be submitted ~~to the competent authorities~~ |  |
| 1185-1189 |  | **Comment:**  The text states, “In accordance with Article 107(3) of Directive 2001/83/EC and to avoid the reporting of duplicate ICSRs, marketing authorisation holders shall only report those ICSRs described in the scientific and medical literature which is not reviewed by the Agency, for all medicinal products containing active substances which are not included in the list monitored by the Agencypursuant to Article 27 of Regulation (EC) No 726/2004.”  **Proposed change:**  Revise lines 1185-1189 as follows, “In accordance with Article 107(3) of Directive 2001/83/EC and to avoid the **~~reporting~~** **submission** of duplicate ICSRs, marketing authorisation holders shall only **~~report~~** **submit** those ICSRs described in the scientific and medical literature **for all medicinal products containing active substances which are not included in the list monitored by the Agency ~~which is not reviewed by the Agency, for all medicinal products containing active substances which are not included in the list monitored by the Agency~~**pursuant to Article 27 of Regulation (EC) No 726/2004. |  |
| Lines 1280-1306 |  | **Comment:** Changes made to this paragraph make this paragraph unclear. Suggested revision is given below.  **Proposed change** (if any): Events may occur, which do not fall within the definition of reportable valid ICSRs, and thus are not subject to the reporting requirements. Even though they may lead to changes in the known benefit-risk balance of the medicinal product and/or impact on public health. These events/observations constituted as emerging safety issues and they should be notified in accordance with the requirements provided in GVP Module IX and not as ICSRs. |  |
| 1512 |  | **Comment and proposed change:** The first row of the table should be removed as it refers to the current EudraVigilance database. In the second row, the text needs to be updated to remove the timing when the new functionalities come into effect. |  |
| 1514-1517 |  | **Comment and proposed change:** This is the only reference to EVWEB. Should this document also outline the requirement for MAHs to download NCA cases from EudraVigilance and provide guidance on frequency of review etc? |  |
| 1548-1553 |  | **Comment:**  The text states, “Only cases of suspected unexpected serious adverse reactions (SUSARs), related to investigational medicinal products (IMPs) or non-investigational medicinal products (NIMPs) studied in clinical trials which fall under the scope of Directive 2001/20/EC (see VI.C.1.1.), should be submitted by the sponsor to the EudraVigilance Clinical Trial Module (EVCTM). The requirements provided in chapter II of EudraLex Volume 10 of The Rules Governing Medicinal Products in the European Union should be applied.”  Chapter II of Eudralex Volume 10 (CT-3) clearly indicates that non-IMPs should not submitted as SUSARs and as such should not submitted to EVCTM (references below):  *— reporting of suspected unexpected serious adverse reactions (‘SUSARs’) to the national competent authority (be it directly or through the Eudravigilance Clinical Trials Module, see section 7.4) and the Ethics Committee (see section 80) […]*  7.2.1. ‘Adverse reaction’ - causality  46.An untoward and unintended response to a non-IMP which does not result from a possible interaction with an IMP is, by definition, not a SUSAR (see also section 7.6). For possible follow-up action, reference is made to section 7.11.3.  7.4. SUSARs reported to the national competent authority (directly or indirectly through EVCTM)  *7.4.1. Introduction*  *63. SUSARs have to be reported to the national competent authority of the Member State concerned.*  *64. In addition, EVCTM has to be populated with these reports.*  *65. In the future, in order to simplify workflows and to avoid duplicate populating of EVCTM, the reporting of SUSARs to the national competent authority should be made for all SUSARs through EVCTM.*  7.6 Adverse reactions *not* to be reported as SUSARs  **-** adverse reactions related not to an IMP but to a non-IMP received by the subject and without interaction with the IMP (see section 7.2.1)  7.11.3. Adverse reactions related to non-IMPs  *119. A serious adverse reaction which is related not to an IMP but to a non-IMP is not a SUSAR and not reported as such (see section 7.2.1).*  Thus, if a suspected adverse reaction to a NIMP should not be submitted to either EVCTM or EVPM, where should they be submitted under the final arrangement?  **Proposed change:**  In VI.C.6.2.1.2., state expectations for submission of suspected adverse reactions to NIMPs. |  |
| 1572-1576  1598-1601 |  | **Comment:** Only those using E2B(R3) will be able to follow the new EudraVigilance business rules and the EU ICSR Implementation guide. Those still using E2B(R2) will only be following revision 2 of the business rules.  **Proposed change** (if any):  The ~~EudraVigilance business rules and~~ EU ICSR Implementation Guide a**nd/or EudraVigilance business rules**. |  |
| 1625-1626 |  | **Comment:**  It seems as reference to G.k.3.1 is missing in the Table for the E2B(R3) part.  **Proposed change** (if any):  Add the following bullet point:   * The data element G.k.3.1 'Authorisation / Application Number' |  |
| 1635 - table |  | **Comment:**  **There are several questions this table raises:**  - Why the difference in requirement for an E2B R2 message compared to E2B R3?  - The 2nd bullet for each?  - For E2B R2 messages Active substance information to be provided based upon ‘all pharmaceutical forms/presentations in the country of authorisation’ whereas for E2B R3 active substance to be based upon active substance(s) that correspond(s) to the composition of the proprietary/branded medicinal product of the country where the reaction/event occurred’  **Proposed change** (if any): Clarification is required here and we wonder whether the Agency will seek to create a new business rule around this differentiation? |  |
| 1635 table |  | **Comment:**  In ICH E2B/R2 bullet 1 *“Data element B.4.k.2.1'Proprietary medicinal product name' should be populated with the medicinal product name as reported by the primary source”* needs to be more detailed for the medicinal product name as reported. Otherwise it could lead to some questions in case of inspection.  **Proposed change** (if any): To be replaced By:  Medicinal Product Name as Reported by the Primary Source' should be populated with the **proprietary/branded** medicinal product name as reported by the primary source; |  |
| 1656 |  | **Comment**: The E2B(R2) bullet point should be consistent with the wording in the E2B(R3) section and make it clear that interacting needs to be completed for all interacting medicines.  **Proposed change** (if any): Data element B.4.k.4.1 ‘Characterisation of drug role’ is to be completed as ‘interacting’ **for all suspected interacting medicines**. |  |
| 1675 |  | **Comment:** What is the rationale for now requesting additional data to be mapped to B.4.k.19? Additional information which cannot be mapped to specific data fields is added to the case narrative. It seems unnecessary to propose changes to E2B(R2) mapping now when everything will be moving to E2B(R3).    **Proposed change** (if any): Suggest removal of all new references to the use of field B.4.k.19. |  |
| 1768 table |  | **Comment:** Detailed information on the use of attachments with E2B(R3) is outlined in the EU ICSR Implementation Guide so it seems unnecessary to repeat it here.  **Proposed change:** Suggest removing the information from this section and adding a reference to the EU ICSR Implementation Guide (pages 33-34). |  |
| 1792-1793 |  | **Comment:** It seems as reference to C.3.2 is missing in the  Table for the E2B(R3) part.  **Proposed change** (if any):  Add the following bullet point:   * Data element C.3.2 'Sender's Organisation' |  |
| 1816-1822 |  | **Comment:** The proposed text may be considered as referring to amendment and not follow-up information (notably typos and MedDRA updates…”  **Proposed change** (if any):  Transfer this paragraph to section VI.C.6.2.2.8 - Amendment report |  |
| Line 1851 (Table) |  | **Comment:** For ICH-E2B (R2), since report amending is not supported, we propose that only cases with impact on its medical evaluation should be submitted applying the same principles as for a follow up report. Non-significant changes (e.g. typographical errors) would be submitted if a new follow-up is received.  **Proposed change** (if any):  In situations, where the amendment of a report is necessary **due to a significant change with impact on the medical evaluation**, the same principles as for a follow-up report can be applied, even where there is no receipt of new information.  In **these** situations where the case is modified ~~without impacting~~ **with an impact** on its medical evaluation, while no new follow-up is received (e.g ~~for correcting a mistake or typographical error~~ **significant amendment of the MedDRA coding**), the date of receipt of the most recent information included in the data element A.1.7 ‘Date of receipt of the most recent information for this report’ should not be changed. |  |
| Table following line 1976 |  | **Comment:** for R2 the table includes mention of the Digital Object Identifier (DOI)for the literature reference. It is my understanding that DOI is an R3 concept not R2.  Would this be also added to the business rule.  **Proposed change** (if any):  *The data element A.2.2 ‘Literature reference(s)’ should be populated with the literature reference.* ***~~The Digital Object Identifier (DOI) for the article should be included where available, e.g.: “International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309-15. doi:10.1056/NEJM199701233360422~~*** |  |
| 2179-2180 |  | **Comment:** Regular ICSR Quality Review by Agency. We would welcome further detail on the expectations for frequency of these reviews  **Proposed change:** A review of the ICSRs quality, integrity and compliance with the reporting time frames will be performed by the Agency at regular intervals **(every six months)** for all organisations reporting to EudraVigilance in line with the Agency’s SOPs. |  |
| 2179-2186 |  | **Comment:** The language in this section is a bit confusing as at one place it mentions that review of the ICSRs for quality will be performed by the agency at regular intervals for all organizations reporting to EudraVigilance and later there is a mention that agency will provide monthly compliance reports. It's not clear if the monthly compliance report will sent to MAH even when there are no quality issues.  **Proposed change** (if any):  Please add whether monthly compliance reports will be issued also if no quality issues. |  |
| 2262 |  | **Comment:** The steps in app 1.1 and 1.2 are the same.  **Proposed change** (if any): Suggest combining app 1.1 and 1.2. |  |
| Appendix 1 |  | **Comment:** According to Appendix 1 there is no mention of the possibility for the MAH to perform follow-up on ICSRs received from EudraVigilance. However, in case of e.g. risk minimisation activities, would it be possible for the MAH to ask for follow-up questions to ICSRs received from EudraVigilance?  **Proposed change** (if any):  Add somewhere in Appendix 1 that the MAH can ask for follow-up on ICSRs received from EudraVigilance.  Furthermore, it will facilitate reading the process flow and the process description, if the numbers used in table VI.2 are added to figure VI2. |  |
| 2267-2272  2276-2280  2285-2289  … |  | **Comment and Proposed change** (if any): It will facilitate reading the process flow and the process description, if the numbers used in table VI.3 are added to figure VI.3  Similar comments for figures VI4, VI5 VI.6, VI.7, VI.8, VI.9, VI.10, VI.11, VI.12, VI.13, VI.14, VI.15 |  |
| 2272 |  | **Comment:** The left most boxes in the business process map are different in VI.3 compared to VI.2.  **Proposed change** (if any): These should be the same. |  |
| 2282 |  | **Comment:** Section 5.1 and 6.1 indicate that when requesting follow-up by an MAH, NCAs should specify the timeframe by which they expect follow-up to be provided. For spontaneous and other sources for which the MAH is not a sponsor or otherwise in any position to exert influence over the reporter though, there is no way the MAH can do more than request the information; they cannot demand answers if the reporter is unwilling, unavailable, busy, or for any other reason not responsive. I would suggest that if follow-up by a particular date is considered essential by the NCA, they should approach the reporter themselves.  The requirement delineated in steps 6.1, 8.2, and 10.2, that MAHs inform the NCA via email whether their follow-up attempts are already ongoing, and whether they are or are not successful, introduces a non-standard element that will be challenging to incorporate into MAHs’ case management processes. Does it actually substantially benefit the NCAs to receive these? If so, of course MAHs will have to find ways to incorporate it—but if the NCAs are not routinely going to *do* anything with this information, it might be better to leave handling of these requests to the MAHs. Outcome of these requests could still be assessed during inspections, and of course any information that is received would still be submitted and available to the NCA in the normal way.  **Proposed change** (if any): Remove references to timeframe; remove requirements for email correspondence from MAH to NCA during follow-up. |  |
| 2282 table section 5.1 |  | **Comment and proposed change:**  To avoid any confusion from MAH, please explain how the local contact is identified: from the EU-registration portal or with sender contacts provided in the E2B sender block.  Proposed change (if any): |  |
| 2282 |  | **Comment:** EFPIA do not feel that it is necessary for MAHs to communicate back to the NCA to say that they have not received any further information. Instead, it should be sufficient that, if significant follow-up is received, that it would be resubmitted to EudraVigilance.  **Proposed change** (if any): Remove steps 8.2 and 10.2. |  |
| 2290 table 5 section 7.1 |  | **Comment and proposed change:**  Please explain how the sender is identified: from the EU-registration portal or with sender contacts provided in the E2B sender block. |  |
| 2290 table 5 section 5 and 8 |  | **Comment:**  EFPIA understand that if batch number is missing after several FU attempts, the case will be loaded but not stored.  The difference between ICSR loaded and stored should be clarified.  **Proposed change** (if any):  Furthermore, if the batch number is not provided in an initial report, it should be mentioned if a negative ACK will be sent.  To avoid any MAH compliance issue, if batch number is missing, the case should be stored once all MAH FU attempts has been completed. |  |
| 2472-2473 |  | Comment: Unclear as to what "where applicable" means here - the references reference the MLM activities. Suggest to reference the MLM guidance or to add more detail here.  Proposed change: this should include ICSRs resulting from the Agency’s **Medical Literature Monitoring** activities in accordance with Article 27 of Regulation (EC) 726/2004. |  |
|  |  | **Comment:** Further clarification required on whether this means that MAHs are not required to send articles on to the EMA if copyright dictates that we cannot.  **Proposed change:** and handling of electronic copies in the frame of regulatory activies. **Where copyright dictates that an article cannot be shared, this should be documented in the case narrative** |  |
| 2585 |  | **Comment:** There are no steps included for cases which may fail transmission from EV to the NCA. We have seen with E2B(R2) cases which are accepted by EV but fail transmission to other EU agencies. |  |
| 2594 |  | **Comment:** Should there be steps included for any cases which fail transmission from the EMA to WHO? |  |
| 2619 |  | **Comment:**  **Example 6:** There is a difference between verifying the existence of a patient and whether or not a valid patient identifier has been provided. These concepts need to be clearly separated.  If, upon follow-up, it is confirmed that there is no patient identifier, this case would be non-valid but should not be nullified. It should also be noted that Health Canada considers a patient valid if the MAH knows that “a patient” exists.  If, upon follow-up, it is determined that the reporter was talking hypothetically and there was no patient, then this case should be nullified.  **Proposed change** (if any): Suggest separating this example into two separate examples; one of a non-valid patient and one where it was confirmed that there was no patient. |  |
| 2620-2626 |  | **Comment:** This sentence is the same as 2627 so can be removed. If it is retained, then the table number needs to be updated.  **Proposed change** (if any):  Examples of scenarios for which ICSRs should NOT be nullified, are provided in Table VI.**15**.~~14~~ |  |
| 2640 section 4.1 |  | **Comment:** Can the timeframe in which MAH should respond to quality findings be indicated as follows: either  **Proposed change** (if any):  “Review draft quality review report and provide comments to EMA within XX days”  Or  “Review draft quality review report and provide comments to EMA within the timeframe requested on receipt of the quality review report”. |  |
| 2654 |  | **Comment:** Step 3. The final sentence on the first paragraph states ‘Are the confirmed duplicates from the same sender organisation or a different sender organisation?’ As there is a Yes/ No question afterwards, the last part of this sentence should be deleted.  **Proposed change** (if any): Are the confirmed duplicates from the same sender organisation ~~or a different sender organisation~~? |  |
| 2665  2681-2691  2697 |  | **Comment:** Confusion in the accountability of the stakeholders between figures and table.  **Proposed change:**   * To avoid any confusion, the title of the column “Responsible organisation should be newly named to “Organisation impacted” * To add an hyperlink be to EMA SOP/WIN |  |
| 2671 |  | **Comment:** The steps in app 7.3 and 7.4 are the same. There is also a lot of repetition within the steps.  **Proposed change** (if any): Suggest combining 7.3 and 7.4. Also propose removing steps 4, 4.1, 4.2 and 4.3 and change the responsible organisation in steps 3-3.2 to NCA/MAH. |  |
| 2716 |  | **Comment:**  **Example 8**: Case scenario with assumed gender. Clarification required - does agency expect MAH to enter 'female' in the appropriate field? This information was not provided by the reporter. At the very least, a comment should be added to narrative to explain that the company has assumed gender of patient is female.  **Proposed change:** Patient is presumably female as suspected product is an oral contraceptive. **(ensure this assumption is captured in the case narrative)** |  |
| 2716 |  | **Comment:**  **Example 12**: As neonate is a qualifying descriptor (e.g. age group), clarify if the reason to consider the example as non-valid case is that several patients do not provide a defined number.  **Proposed change** (if any): Change validity assessment column as followed:  Patient’s qualifying descriptor available  No definite number of patients |  |
| 2716 |  | **Comment:**  **Example 13**: Please clarify that the case is non-valid since it is second hand information. Nowhere else in the document is second hand information described? In addition a case from a newspaper can be a valid case even though it is quite often second hand information.  **Proposed change** (if any):  Mention second hand information in section VI.A.2.3. **Primary source** | Relevant? |
| 2716 |  | **Comment:**  **Example 15** describes a report of 50 patients who developed ovarian cancer, but is classified as non-valid on the basis no patient identifiers are provided. Onset of ovarian cancer should be sufficient to conclude that all 50 patients are however female, and therefore valid. It would be interesting if it is recommended to create 50 invalid cases while performing FUP or if 1 invalid ICSR would be enough.  **Proposed change** (if any): Clarification / correction of examples.  **~~Non-valid~~ Valid case**. Identifiable reporter and qualification. Report describing definite number of patients with **~~no~~** qualifying descriptor available for each patient **(gender).** Report should be followed up as possible. |  |
| 2716 |  | **Comment:** Suggestion for addition of examples to differentiate solicited vs spontaneous ICSRs.  For example, patient is not yet enrolled in a Patient Assistance Program but during the application process, the MAH learns that the patient is already on MAH product X and was hospitalized for pancreatitis. Is this a solicited, spontaneous or non-case?  Please find below some scenarios that could be included:  **Example 16:**  A patient calls regarding their application for enrollment in the company’s financial assistance program. During the call, the patient mentions that they have been on your product for years and was recently hospitalized for pneumonia  Validity assessment:  Spontaneous report because the patient is not yet enrolled in the program.  **Example 17:**  A physician writes on behalf of a patient urging the company to continue the patient’s enrollment in their financial assistance program as the patient is unable to work due to blindness.  Validity assessment:  Solicited report because the patient is enrolled in the program. Reporter causality of unknown unless follow-up information indicates otherwise.  However, if the physician clarifies that the blindness is medical history, it is a non-case.  **Example 18:**  A company reaches out to a physician with notification that the patient’s enrollment in a patient support program is due to expire and reapplication is required. During the call, the company learns that the patient has died. The physician stated that the death was not related to company medication.  Validity assessment:  Solicited report because the patient was enrolled in the solicited program at the time of death. Reporter causality of not related.  **Example 19:**  A patient is enrolled in a patient support program for company product X. During a call with the company about product X, the patient mentions that they had an adverse event due to product Y (also a company product), which is not part of the solicited program.  Validity assessment:  Creation of 2 linked reports:   * Solicited report with suspect product X and a reporter causality of not related * Spontaneous report with suspect product Y   **Example 20:**  As part of the application process for a patient support program, the patient’s physician submits copies of medical records (not required for enrollment) which list multiple health conditions without an association to the company product.  Validity assessment:  Non-case  **Example 21:**  Suggest adding example “real person” behind reports from internet or digital media.  **Example 22**:  Place here the example from the core text line 514  “Two patients experienced nausea with drug X …” should not be considered valid without further information".  **Example 23**:  Add example for “one patient” or “a patient” - Please clarify whether a report should also be considered non-valid and not submitted if the reporter only mentions "one patient" or "a patient"… |  |

1. Editorial change comments on text

| Line number(s) of the relevant text  *(e.g. Lines 20-23)* | Stakeholder number  *(To be completed by the Agency)* | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome  *(To be completed by the Agency)* |
| --- | --- | --- | --- |
| 192-298 |  | **Comment:** It would be useful to cross reference the relevant section here.  **Proposed change** (if any): Insert “(See VI.B.6.3) after sentence ending “…submitted as individual case safety report”. |  |
| 199 |  | **Comment:** Please rephrase in order to align with the rest of the document.  **Proposed change** (if any):  Please change: “Section B of this Module highlights the general…” to: “Section VI.B highlights the general…” |  |
| 713-716 |  | **Comment:** Incorrect P module referenced. P IV is geriatric population according to EMA website, not paediatric as stated here. Paediatric supplementation is not discussed on the EMA website. |  |
| 805-808 |  | **Comment:** Incorrect reference.  **Proposed change** (if any): ICSRs nullification in line with ICH-E2B is provided in VI.C.6.2.2.9 |  |
| 980 |  | Spelling: rational  Change to rational**e** |  |
| 1444 |  | Typo, reference should be App3.1 and App3.2 |  |
| 1532 |  | Table below, second record should be light blue to not dark blue |  |
| 1748 |  | Typo , remove the point between used to present |  |
| 1794 |  | Typo; delete “s” in reactions: “a new suspected adverse reaction~~s~~,” |  |
| 1955 |  | **Comment:** This states parent’s characteristics instead of patient’s characteristics.    **Proposed change** (if any): patient’s characteristics |  |
| 2605 |  | **Comment:** Incorrect table reference.  **Proposed change** (if any): Examples of scenarios for which ICSRs should also be nullified, are provided in Table VI.14 |  |
| 2281 |  | **Comment**:  Third column, second row contains a typographical error, “Receipt of a report of a suspected adverse reaction related to a medicine (ISCR).” ISCR should be ICSR.  **Proposed change:**  Correct third column, second row as follows, “Receipt of a report of a suspected adverse reaction related to a medicine **~~(ISCR)~~ (ICSR)**”  **Ensure that references to “ICSR” are appropriately referenced throughout the document.** |  |
|  |  |  |  |

1. Topic Out of scope comments on text

| Line number(s) of the relevant text  *(e.g. Lines 20-23)* | Stakeholder number  *(To be completed by the Agency)* | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome  *(To be completed by the Agency)* |
| --- | --- | --- | --- |
| 396-399 |  | **Comment:** It is not clear whether the phrase ‘where adverse events reporting is actively sought’ refers to whether an organised data collection system must specify that ‘adverse events’ are being actively sought or whether it refers to an organised data collection system in which data from patients/HCPs/consumers is being actively sought (and therefore ‘adverse events may be collected in the process). For example, the protocol for a survey might specify that only questions about the efficacy of a product are to be asked, but in the process, ‘adverse events’ may be collected – are those adverse events ‘solicited’ (VI.B.1.2 may need to clarify this), even though the programme actively solicits only efficacy data? Should we add here also report from internet sources if internet /social media channels are not used as a channel of conducting organized data collection program?  **Proposed change:** In this aspect, the following situations should also be considered as spontaneous reports:   * Reports collected from internet sources if internet/social media channels are not used as a proactive channel for collecting safety information (analogous to how literature adverse events are considered spontaneous) |  |
| 433-435 |  | **Comment:** Please clarify what is meant by '**considered'** If multiple medicinal products are mentioned in the publication, only those which are identified by the publication's author(s) as having at least a possible causal relationship with the suspected adverse reaction should be **considered** by the concerned marketing authorisation holder(s).  **Proposed change:** should be considered **as suspect** by the concerned marketing authorisation holder(s) |  |
| 459 |  | **Comment:** Clarification would be an huge add value on how should **owned** digital media be defined.  **Proposed change:** Marketing authorisation holders may also consider utilising their websites (i.e., site is owned by the Company or Company has authority over the final material content) to facilitate the collection of reports of suspected adverse reactions. |  |
| 1155-1157 |  | **Comment:** The wording "Where this opinion is missing, the marketing authorisation holder should exercise its own judgement based on the information available in order to decide whether the report is a valid ICSR", is not consistent with the wording in Table VI.1 - **perform causality assessment**  **Proposed change:** Where this opinion is missing, the marketing authorisation holder should ~~exercise its own judgement~~ **perform its own causality assessment** based on the information available in order to decide whether the report is a valid ICSR,.. |  |