9 December 2016
EMA/847133/2016

Comments received from public consultation on good pharmacovigilance practices (GVP)

GVP Module VI – Management and reporting of adverse reactions to medicinal products (EMA/873138/2011 Rev.2)

The draft of this module was released for public consultation between 8 August 2016 and 14 October 2016. The module has been revised, taking the comments received into account.

Those who participated in the public consultation were asked to submit comments using a specific template.

The comments received are published, identifying the sender's organisation (but not name). Where a sender has submitted comments as an individual, the sender's name is published.

The European Medicines Agency thanks all those who participated in the public consultation for their contributions.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<14th October, 2016>

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

Comments from:

Name of organisation or individual
AEFI

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 number *(To be completed by the Agency)*	General comment
	a. Literature reports: Marketing authorisation holders are therefore expected to maintain awareness of possible publications through a systematic literature review. The European medicines Agency monitors the Medical Literature daily for a number of substance published in their website. Nevertheless, this action seems that do not get rid MAH of the work they were doing before and should continue monitoring the widely used databases no less frequently than once a week. Due to the lack of serious adverse events that occurred with products that are well known, MAH who commercialized products referred to Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended, should be exempted of this frequency and extend it at least to: "not less than once every 15-30 days". b. To define what is "accurate and verifiable data for the scientific evaluation". c. Medicinal products falling out of scope of Article 57(2) of Regulation (EC) No 726/2004 legal obligations include: Traditional use registration application for a herbal medicinal products (Article 16a of Directive No 2001/83/EC) • Simplified registration application for a homeopathic medicinal products (Article 14 of Directive No 2001/83/EC) • Medicinal products authorised outside the EEA or following a non-EU procedure. Marketing authorisation holders shall submit all serious ICSRs that occur in the EU or outside the EU to the EudraVigilance database only. But, non-serious cases just for products that occur in the EU. In this terms, Traditional use registration application for a herbal medicinal products (Article 16a of Directive No 2001/83/EC) and simplified registration application for a homeopathic medicinal products (Article 14 of Directive No 2001/83/EC), Shall be also medicinal products falling down from the need of the submission of NON-SERIOUS adverse events as they are not declared through the XEVPRM.

2. Specific comments on text

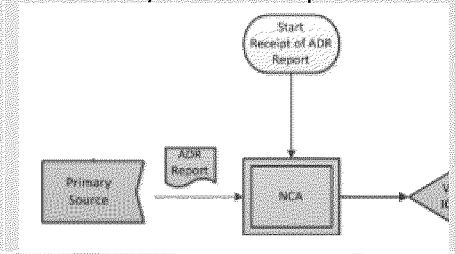
Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 238-243		Comment: In order to help or avoid possible confusion coding between off label use and misuse, it should be very helpful to provide examples for off label use and misuse or to include the reference of the draft related to the proposal for the collection and reporting of information on off-label use by Marketing Authorisation Holders (MAHs): *Reflection paper on collecting and reporting information on off-label use in Pharmacovigilance-EMA/293194/2016.* Proposed change (if any):
Lines 312 - 313		Comment: The sentence "In case of multiple sources, it identifies the source of the worldwide case unique identification number by defining the country where the case occurred." is contradictory with the information published in the Spanish Royal Decree 577/2013, of July 26 by the Spanish Agency of Medicines and Medical Devices: article 9, section 3 (b) "For suspected adverse reactions reported by healthcare professionals practicing in Spain or by citizens who are in Spain, the marketing authorization holder shall include information identifying the Autonomous Community where the reporting healthcare professional practices or the reporting citizen resides, respectively." We suggest to clarify this contradictory point with the Spanish Health Authority (AEMPS) in order to clarify this sentence with the aim to avoid inconsistencies in the future. Proposed change (if any):
Line 362-364		Comment: In the sentence "ICH ICSR uses Nullflavour code sets from the HL7 Messaging Standard primarily to classify the set of source data situations that may give rise to a missing value". An ICH is mentioned ("ICH ICSR") however the ICH reference code is not explicitly provided, could it be possible to include the complete reference of the ICH?.

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')*
		Proposed change (if any):
Lines 395-397		Comment: The sentence: "It does not derive from a study or any organised data collection systems where adverse events reporting is actively sought, as defined in VI.B.1.2." might lead to think that solicited reports are only those where adverse event reporting is actively sought. However definitions in section VI.B.1.2. do not make any references to actively seeking adverse events. Adverse event collection is an important part of any patient support program or market research activity however it is not the primary goal. The key for categorizing reports as solicited, as per lines 473-479, is whether they originate from organised data collection systems and not whether adverse events are sought. Proposed change (if any): It does not derive from a study or any organised data collection systems ~~where adverse events reporting is actively sought~~, as defined in VI.B.1.2.
Lines 413-415		Comment: In line 414 the term "*country*" is used however in line 484 for the same information is used "*Member State*". We suggest to use the same term in both sentences ("*country*" or "*Member State*"), in order to unify concepts. Proposed change (if any):
Lines 421-423		Comment: Due to the lack of serious adverse events that occurred with products that are well known, MAH who commercialized products referred to Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended, should be exempted of this frequency and extend it at least to: "*not less than once every 15-30 days*".

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')*
		Proposed change (if any): 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. *MAH who commercialized products referred to Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended, are exempted of this frequency and extend to not less than once every 15-30 days*.
Line 430		Comment: In section **VI.B.1.2 Literature reports,** the concept "draft manuscripts" is mentioned in line 430. We suggest to include a definition of "draft manuscript" in order to clarify when a literature report is considered draft. For example, in the following situations it could be not clear whether the case should be considered a literature case or an spontaneous case: - The draft was sent to a journal but it is not known if the journal accepted it; - The article was sent and accepted by the journal but it has not been published yet. For all the above situations, should the article be considered as a literature case or as an spontaneous case? after the publication of the article, should the case be updated and classified as a literature case? Proposed change (if any):
Lines 483-485		Comment: In line 484 the term "*country*" is used however in line 414 for the same information is used "*Member State*". We suggest to use the same term in both sentences ("*country*" or "*Member State*"), in order to unify concepts. Proposed change (if any):
Lines 530-531		Comment: In the sentence "In this particular situation, medical judgement should always be applied in deciding whether the notified information is an adverse reaction or an event" is mentioned: "*medical judgment*".

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')*
		Comment: A comment should be added in order to clarify if the "*medical judgment*" is referred only to Healthcare professionals' judgment or if the MAH's *medical judgment* could be also considered valid for that purpose. Proposed change (if any):
Line 939 - 941		The sentence is "They should be notified by the primary source to the competent authority in the Member State where the reaction occurred or to the marketing authorization holder of the suspected medicinal product, but not to both (to avoid duplicate reporting)." Comment: We suggest to specify who is considered the primary source, the investigator or the sponsor (as it is specified in previous section VI.C.1.1 Reporting rules for clinical trials, see line 915). Proposed change (if any): They should be notified by the primary source (the investigator or the sponsor) to the competent authority in the Member State where the reaction occurred or to the marketing authorization holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).
Lines 1099-1101		Comment: One of the responsibilities of the MAH is to establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports. This should depend on the seriousness of the cases. Moreover, it is not well explained what it is an accurate and verifiable data and how it should be managed. Proposed change (if any):
Line 1105		Comment: The sentence "All these reports of suspected adverse reactions shall be accessible at a single point within the Union" should be clarified regarding whether the cases shall be accessible at a unique point (within UE) or they could be accessible at different points. In addition, it should be clarified if the term "report" means also the

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')*
		source document of the case. Proposed change (if any):
Lines 1437-1458		Comment: Traditional use registration application for a herbal medicinal products (Article 16a of Directive No 2001/83/EC) and simplified registration application for a homeopathic medicinal products (Article 14 of Directive No 2001/83/EC). Shall be also medicinal products falling down from the need of the submission of NON-SERIOUS adverse events as they are not declared through the XEVPRM. Proposed change (if any):
Line 1795		Comment: The word "reactions" should be in singular: reaction Proposed change (if any): relates to, for example, a new suspected adverse reaction, a change in the causality
Lines 2179-2186		Comment: In this paragraph the following information was included: "For the purpose of the monitoring of the 15 or 90 days reporting time frames, the Agency provides competent authorities in Member States and marketing authorisation holders with monthly compliance reports." Regarding to compliance with the reporting time frames it should be specified if the amendment reports will be considered into the monthly compliance reports. Proposed change (if any):
Line 2271		Comment: It appeared 2 different "*Primary Sources*": Consumer and Healthcare professional, instead indicating only one:

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')*
		Primary Source Proposed change (if any): ~~Consumer / Healthcare professional~~ Primary Source 
Line 2274		Comment: In table VI.3 (step 13) it states that the Responsible Organisation is MAH. We suggest to change MAH by NCA. Proposed change (if any): ~~MAH~~ NCA
Line 2289		Comment: Figure VI5 includes the term "*receiver*", could it be possible to include details to clarify who is a possible receiver? Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 October 2016

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

Comments from:

Name of organisation or individual
The Association of the European Self-Medication Industry (AESGP)

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 number *(To be completed by the Agency)*	General comment
	AESGP welcomes the fact that reporting of emerging safety issues has been taken out of this module (now covered more appropriately in GVP Module IX) with reference to VI.A.1 Scope (lines 182-195) and VI.C.2.2.6 (lines 1279-1306). Consideration should be given to make the revised module effective consistently with timelines for EudraVigilance Change Management. This is especially important for the proposed deleted text on interim reporting arrangements (Lines 1396-1430) and information included on E2BR2 and E2BR3 requirements.

2. 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')*
238 - 240		**Comment**: The definition of Off-label use in the draft module [*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*] differs from the definition in the MedDRA Term Selection: Points to Consider document (page 49) [*the concept of "Off-label use" relates to situations where a healthcare professional intentionally prescribes, dispenses, or recommends a product for a medical purpose not in accordance with the authorised product information*]. The definition is also different from Annex 1 of GVP Module. It is not clear which definitions should be used by MAH, especially since in section VI.B.8. 'Reporting modalities', the instruction is to adhere to MedDRA Term Selection: Points to Consider Document with regard to the content and format of electronic ICSRs.
244 - 246		**Comment**: The definition of Abuse in the draft module [*This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects [DIR Art 1(16)]*] differs from the definition in the MedDRA Term Selection: Points to Consider document (page 36) [*Abuse is the intentional, non-therapeutic use by a patient or consumer of a product – over-the-counter or prescription – for a perceived reward or desired non-therapeutic effect including, but not limited to, "getting high" (euphoria). Abuse may occur with a single use, sporadic use or persistent use of the product*]". The definition is also different from Annex 1 of GVP Module. Therefore it is not clear which the MAH should use, especially since in section VI.B.8 the instruction is to adhere to MedDRA Term Selection: Points to Consider Document with regard to the content and format of electronic ICSRs.
299 - 310		**Comment:** Two definitions are given, one for "primary source" and the second for "primary source for regulatory purpose". Can you please precise if these sections in E2B(R3) for both are different as it seems that we have not to

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')*
		populate these fields in the same way.
500 - 501		**Comment**: Is this the intention to require adding at least one parameter of either name, address or phone number supplied in the identifiable reporter as a new business rule? **Proposed change** (if any): If this is the case, this should be clarified and refer to in the sentence.
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 November 2017? **Proposed change** (if any): Add reference to business rule with this clarification.
501 -507		**Comment:** There is a discrepancy between lines 501/502 and 506. Lines 501/502: 'An ICSR should not be considered valid for reporting unless this information is available for at least one reporter'. Lines 506/507: 'All parties providing case information or approached for case information should be identifiable, (not only the initial reporter);' **Propose changes** (if any): Please specify if is sufficient to have only one reporter among several identifiable or if all reporters should be identifiable.
806 - 808		**Comment:** Please add to the example provided "in case of duplicate reports" to be as complete as information reported on VI.C.6.2.2.9 **Propose changes** (if any): The nullification of a report should be used to indicate that a previously transmitted ICSR is considered completely void (nullified), for example when the whole case was found to be erroneous in case of duplicate reports. Guidance on ICSRs nullification in line with ICH-E2B is provided in VI.C.6.2.2.~~109~~.
1279		**Comment:**

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')*
		As now ESI is out of scope of this module and as it is transferred to module IX, it would be relevant to transfer this paragraph to part IX.A.1 of module IX but without deleting the examples of ESI
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.
1635 (table)		**Comment**: Why is there a difference in requirement for an E2B(R2) message compared to E2B(R3) notably regarding the 2nd bullet? Indeed for E2B(R2), the active substance information is to be provided based upon 'all pharmaceutical forms/presentations in the country of authorisation' whereas for E2B(R3) the information is 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): A clarification is required. Will the EMA seek to create a new business rule around this differentiation?
1728 - 1731		**Comment**: Lines 1728 to 1731 should be deleted as it refers to the part on 'interim arrangements' which was removed **Proposed changes** (if any): ~~During the interim arrangements (see VI.C.4.1), the case narratives included in the ICSRs submitted to the competent authorities in Member States by marketing authorisation holders, should not be modified or deleted when the ICSRs are forwarded to the EudraVigilance database by the competent authorities~~.
1851 – 1852 (table)		**Comment**: The wording should be changed in order to be aligned with rev.1.

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')*
		Proposed change (if any): The data element C.1.5 'Date of Most Recent Information for This Report' should remain ~~unchanged~~be changed to the date when corrections are made.
1976 (table)		**Comment:** Is the Digital Object Identifier (DOI) a mandatory piece of information? Would this be also added to the business rule?
2281 – 2283 (table VI.4)		**Comment**: Could it be clarified in the table cases which will be followed up by contacting the QPPV and case which will be followed up by contacting local contact person (point 5.1)?
2605		**Comment**: Please replace table VI.13 by VI.14 **Proposed change** (if any): Examples of scenarios for which ICSRs should be nullified, are provided in Table VI.~~13~~14..
2619		**Comment**: As per Table VI.14, if we have all elements except patient identification, in this situation, the case should still be recorded in the safety data base.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016

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

Comments from:

Name of organisation or individual
Baxter Healthcare Corp.

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*).*

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	none

2. 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')*
410-412		Comment: While ICSR from PSP/MRP are solicited, there is a subset where a consumer/HCP who is participating in a PSP/MRP may call in an ICSR. In this case they are spontaneously calling in the AE rather than it being solicited through the organized collection of data. Proposal for modification. Proposed change (if any): Reports of suspected adverse reactions in relation to those adverse events for which the protocol of non-interventional post-authorisation studies or Patient Support and Market Research Programs provides differently and does not require their systematic collection
472-493		Comment: Suggestion to add in one more exception bullet point to the section. Proposed change (if any): • suspected adverse reactions originating from groups such as general customer service centers, medical information or technical service (solely for the purpose of handling product orders, customer queries and repairs across the MAH's portfolio of medicinal products) or refill prescription programmes where there is no active collection of adverse events occurring
480-482		Comment: Modification as described above Proposed change (if any): Reports of suspected adverse reactions in relation to those adverse events for which the protocol of non-interventional post-authorisation studies or Patient Support and Market Research Programs provides differently and does not require their systematic collection.
537-538		Comment: The only types of non-valid cases that can have on-going safety evaluation are those that have at least a drug-AE combination. Suggestion to narrow down. Proposed change (if any): Reports, for which the minimum information is incomplete, should nevertheless be

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')*
		recorded within the pharmacovigilance system for use in on-going safety evaluation activities when there is at a minimum a drug-AE combination or drug and one of the following: overdose, abuse, off-label use, misuse, medication error or occupational exposure.
574-577		Comment: Follow-up on a case should not solely be done for age, the reporter may not be as receptive. Proposal for addition below. Proposed change (if any): The provision in ICSRs of patient's age information is important in order to be able to identify safety issues occurring specifically in the paediatric or elderly population. All possible efforts should be made to follow-up on an individual case to obtain age information of the patient, where it is initially not reported by the primary source, if there are other reasons that the ICSR requires follow-up.
589-594		Comment: It is important to obtain consent for follow-up with HCP since many times the consumer has limited information. Addition proposed. Proposed change (if any): When information is received directly from a consumer suggesting that an adverse reaction may have occurred, if the information is incomplete, attempts should be made to 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. If MAH has consent to follow-up with the nominated HCP this should be the primary source for follow-up information.
1954-1956		Comment: There appears to be confusion between patient and parent characteristics. Since item c. applies to reports with no reaction affecting the child, only patient characteristics (i.e. mother or father) should be relevant. Proposed change (if any): The parent-child/foetus report does not apply; i.e. ~~the parent's characteristics only apply~~ the section patient characteristics should be populated with data for the parent (mother or father) who experienced the suspected

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')*
		adverse reaction.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016

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

Comments from:

Name of organisation or individual
BPI Service GmbH

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 number *(To be completed by the Agency)*	General comment	

2. 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')*
Lines 238 – 246 and 251-252		Comment: For the purpose of clarity, it would be desirable to include in these definitions the important distinctions between Off-label use, Misuse, Abuse and Medication Error, in line with MedDRA Points to Consider v19.1 (p35-36), if indeed these definitions are endorse for GVP VI? Specifically "By Whom"; patient/consumer or healthcare professional and if therapeutic use or not. Proposed change (if any): ***Off-label use:*** This relates to situations where the medicinal product is intentionally ~~used~~ prescribed by a healthcare professional for therapeutic use for a medical purpose not in accordance with the terms of the marketing authorisation. ***Misuse:*** This refers to situations where the medicinal product is intentionally and inappropriately used by a patient/consumer for therapeutic use not in accordance with the terms of the marketing authorization . ***Abuse:*** This corresponds to the persistent or sporadic, intentional excessive use by a patient/consumer for the non therapeutic use of a medicinal product, which is accompanied by harmful physical or psychological effects [DIR Art 1(16)]. ***Medication error:*** This is an unintended failure in the drug treatment process while the medication is under the control of a healthcare professional or patient/consumer that leads to, or has the potential to lead to harm to the patient2.
Lines 1213-1214		Comment: Please could you clarify what is meant by point e. in the exclusion criteria for ICSRs published in the scientific literature? This can be generally interpreted as ICSRs from all published studies for licensed substances can be excluded for reporting, was that the intention? If not, clarification as to exactly which studies can be excluded is needed, eg sponsored by other MAHs vs investigator initiated studies/academia? etc., and guidance on which data is accepted for exclusion, eg in the absence of a clearly named sponsor or trade name, would author affiliation be sufficient?
Table VI.21 No 6.2 (Line 2700) and Table VI.22		Comment: Although we like the idea of a central mailbox to report detected duplicates, it is confusing to have 2 separate email addresses depending on whether the duplicate was detection at the point of signal detection or not. Is this necessary or is it possible to have only one Email address?

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')*
No 3.1 (Line 2711)		
Table VI.23 No 8 (Line 2716)		Comment: We disagree with the assessment of this example as a valid case. An assumption on gender cannot be made in light of the possibility of off label use or misuse. Follow up, however, would certainly be necessary in this case.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14-Sep-2016

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

Comments from:

Name of organisation or individual
CSL Behring – GCSP Case Management

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*).*

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	

2. 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')*
251 – 252		Comment: Request for clarification of wording: "This is an unintended failure in the drug treatment process …" Proposed change (if any): The above reads as if referring to a lack of effect or lack of compliance. Please be more specific.
408 – 409		Comment: Request for clarification. If we receive an AE for a patient as part of a patient support program (solicited) and in addition we would receive information on the same patient and same event from an unsolicited source at a later point in time (patient's regular physician) we should ignore the solicited report and handle the entire situation as spontaneous? Proposed change (if any):
1235 – 1246		Comment: Clarification: Currently we consider all suspected or confirmed falsified medicinal product reports as serious – serious criteria "Medically important" even if no adverse reaction occurred or as linked to the reported reaction. Is this in accordance with the regulation or would we only be required to report ICSRs of falsified products with serious reactions? Proposed change (if any):
1851 – 1852		Comment: Request for clarification of wording "The principle of amending a report as such is not supported. In situations, where the amendment of a report is necessary, the same principles as for a follow-up report can be applied, even where there is no receipt of new information. It should be noted that this can lead to situations, where these reports may appear as "late reports" i.e. do not meet the established reporting timelines." – Please explain. Proposed change (if any):

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')*
1908 – 1909		Comment: Request of clarification. Should the original verbatim text always appear beside the English summary within the case narrative? Currently this is only required for serious spontaneous cases from Spain – all other cases are processed in English only. This change would have major impact on case processing, data base configurations and resources. Proposed change (if any):
2716 – Example		Comment: Request of clarification because the logic between the example 8 and 14/15 is unclear. Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

09-Aug-2016

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

Comments from:

Name of organisation or individual
[redacted]

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*).*

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment

2. 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')*
437-440		Comment: In these lines is stated that the first publication author should be considered as the primary source. However, on many scientific and medical publications, the first author does not always represent the "corresponding author" (i.e. the author to whom any information, query, revision, etc. on a paper contents should be directed), often found in the last position. In my opinion, the "corresponding author" (when clearly identifiable) should represent the primary source for a literature ICSR. This might facilitate the obtainment of follow-up information, since the email address and contact details of the corresponding author are usually always present on the first page of the relevant publication. Proposed change (if any): Relevant medical information should be provided and the ~~first~~ corresponding publication author (or the first author, in case a corresponding author is not specified) should be considered as the primary source as well as the primary source for regulatory purposes in line with 440 ICH-E2B(R3) (see VI.A.2.3.).

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

Name of organisation or individual
The Danish Medicines Agency (DKMA), Pharmacovigilance and Medical Devices [redacted]

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*).*

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment

2. 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')*
Page 26, line 910-920, Page 44, line 1547-1560, Page 71, line 2060-2064, Page 73, line 2099-2113		Comment: It is described in the Rev. 2 of GVP Module VI that only cases of SUSARs related to IMPs or NIMPs studied in clinical trials which fall under the scope of directive 2001/20/EC should be submitted by the sponsor to EVCTM. It is also described in Rev. 2 that ADRs only suspected to be related to a drug other than IMP and NIMP should reported as spontaneous. According to directive 2001/20/EC article 17.3(A): Each member state shall see to that all SUSARs related to IMP which are brought to its attention are immediately entered to EVCTM. Proposed change (if any): Since only SUSARs related to IMPs are to be entered into EVCTM, the DKMA finds that the change regarding reporting of SUSARs related to NIMPs is not correct. To make sure that ADRs related to NIMPs and other drugs besides from IMPs are reported the DKMA suggests, that these in the future will be reported as spontaneous reports, as they have been until now.
App. 8, table VI.23, no 15		Comment: The example says that this is a non-valid case, since the case describes a definite number (50) of patients with no qualifying descriptor available for each patient. Since the patients developed ovarian cancer, the patients must all be female. Don't we the have 50 valid cases (gender: female)?
Page 129, line 2626		Comment: According to the text scenarios for which ICSRs should not be nullified refers to table VI.14.

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')*
		Proposed change (if any): The reference should be table VI.15.
App. 7.1, fig. VI.10, table VI.17 Table VI.17, no 2.3		Comment: In case the sender disagrees with EMA regarding the duplicates and do not think they are duplicates. What to do then? Are the confirmed duplicates from the same sender organisation or a different sender organisation, is not a yes no question and the DKMA will therefore propose that it is changed to: "Are the confirmed duplicates from the same sender organisation?".
App. 7.2, fig. VI.11, table VI.18 Table VI.18, no 8.1		Comment: It is described that the NCA will be able to receive the master via rerouting. It is unclear if a nullification request will be sent to the NCA for the duplicate. The DKMA would like to receive a nullification of the duplicate case as it is described in table VI.19, no. 4.2. Responsible organisation should be EMA not sender organisation.
App 7.4, fig. VI.13, table VI.20		Comment: The DKMA sees a big problem with the proposed procedure. If both MAHs and NCA are responsible for merging the duplicates, there is the possibility that the different senders will identify the duplicates on the same day and merge them simultaneously. If NCA dedicates case A as master case and merges case B into case A, case B will be nullified (and nullification of duplicate B will be sent to the EV database), and case A remains as master case (and the only valid case).

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')*
		If MAH B dedicates case B as master case and merges case A into case B, case A will be nullified (and nullification of duplicate A will be sent to the EV database), and case B remains as master case (and the only valid case). In this example nullifications of both the cases (case A nullified by MAH B, case B nullified by NCA) will be sent to the EV database and therefore no valid case will exist. Will master cases merged by MAHs be rerouted to NCA and will NCA receive a nullification regarding the duplicates? Proposed change (if any): The DKMA proposes that the NCA should be responsible for duplicate merging. If an MAH detects a duplicate, they can notify the relevant NCA and the NCA will (if they agree) merge the duplicates.
App. 7.5, fig. VI.14, table VI.21		Comment: Is App. 7.5 a summary of App. 7.1, 7.2, 7.3 and 7.4? If it is, it is very confusing. It is described that if the MAH/NCA detects a duplicate where one is received directly from primary source and one is from EV the ICSR from the primary source should be updated with the case number of the case received via EV and be retransmitted to the EV. After that EMA proceeds as outline in fig. VI.11. Why does the process proceed as outlined in fig VI.11. Isn't this the process described in fig. VI.13 (duplicates from different sender organisations detected by sender organisation)? The description in "start" contradicts the description in no.1 and does not correspond to fig. VI.14. Is the scenario described in table VI.21 no.5 the same scenario as described in VI.App.7.3, fig. VI.12? If yes, it would be nice if there in the box ("Update one ICSR, nullify the other ICSR(s) & report all previously reported duplicates to EV") in fig. VI.14 is referred to VI.12.

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')*
Table VI.21, Start Table VI.21, no 5 Tabel VI.21, no 5.2.1		Why should the master case created from the duplicates not be sent to EV? If the duplicates are nullified there will no longer exist any case. If MAH nullifies both duplicates and does not transmit the master case to EMA. How will the NCA receive the master case?

Please add more rows if needed.

COMMENTS ON GVP VI.A FROM [redacted]

Page 7, line 241

Suggest adding to the definition that misuse could or may cause harm and that there is no evidence at all to support such misuse. If it harm is not an issue why should we worry about it?

Page 7 line247

Occupational exposure could occur to a medicine in transit. Exposure is always unintentional so worth adding this before 'exposure'

Page 10, line 340

Is adverse events meant here or adverse reactions? If events then worth emphasising application to AE management in clinical trials

Page 11 Section VI.B.1.1.1

Line 395 A spontaneous report may also contain unrelated adverse events and product complaints

Lines 396-7 Is active solicitation an essential ingredient of 'organised data collection'? If so, then definition should clarify

P405-7 What happens to feedback from solicited report initially classified as unrelated and then becoming related with follow up

Line 410-412 Suggest use the word coincidental for such cases of ADRs that arise outside the protocol

Line 414-415 Do not suggest using such wording about active collection as this may well discourage to discourage

Page 12 Section VIB.1.1.2

What about other benefit-risk information apart from ICSRs?

Line 427 For local literature search, should there be not just a M.A. but also, a product launch? Logically, it would be futile searching if no product was reaching patients

Line 432 What about cases from interventional clinical trials? Should only suspected ADRs be added or should all AEs or SAEs be captured on the PV database?

Line 458 We suggest MAHs should utilise websites to facilitate reporting rather than 'may'

Line 474 We suggest that organised data collection systems refer to collection of information for scientific or medical purposes

Line 520 Should the explicit statement excluding a relationship of a reported AE be in writing or is verbal adequate?

Line 525 As well as no information on the type of ADR, should incomprehensible medical terms and/or sense also mean that a case does not qualify as a valid ICSR?

Line 526 Does no further information about the clinical circumstances also include fatal outcome when it is reported alone?

Line 530-33 If medical judgement concludes that what was thought to be an ADR , is in fact disease progression or relapse should this classified as an unrelated AE or a case of lack of effect?

Line 553 A HCP may says that the diagnosis the patient claims, is not in fact correct and/or misinterpreted.

Lines 602-605 It is uncertain what value these sentences have as it is stating the obvious that follow up is not possible if a report is anonymised and so may not be a case.

Line 648 Whereabouts should the source data be accessible? We assume it is acceptable if source data is stored locally at the country level.

Line 657 When and how should proficiency of data entry staff be confirmed? Should this be before data entry occurs unsupervised?

Line 686 Should 'all' congenital anomalies be regarded as serious? Medical manifestation may occur at any age and attributed to exposure in pregnancy not just children.

Line 698 Should this signal of a teratogenic effect be validated or confirmed or just a signal?

Line 724 Medication error resulting in off label use or overdose or occupational exposure but no actual ADR? Might that be expeditable case?

Line 744 Might it be helpful to expand on meaning of 'critical'? For example, does it refer to therapy for a potentially disabling or life-changing indication for which there is no other authorised therapy?

Line 762 When referring to signal should it be validated and/or confirmed?

Line 770 Does this include partners who are 1) in a co-marketing arrangement 2) independent MAHs?

As written, it implies not especially if partner is independent and they are in a co-licensing arrangement.

Line 781 When does awareness by whom start? How is awareness defined? For example, an abstract in a foreign language identified by a partner? Should it be up to the discretion of the MAH to define these points in agreements? Might awareness by MAH only occur once English translation is available that MAH can understand?

Line 797 Partners are not mentioned as mentioned in comment referring to Line 770.

Line 807 It is not a whole case that could be erroneous (such as when there turns out to be no ADR at all and so no case at all) but also one of the critical components that makes case valid could be wrong making a case invalid for the purposes of expedited reporting

Line 855 What happens if an ADR is reported to a NIMP which happens to be an EU authorised medicine? Should corresponding MAH be informed?

Line 861 What happens if there is no open EU CTA for an EU authorised product while there are interventional trials ongoing outside the EU generating SUSARs? This would include emergency INDs in the US? As written expedited ICSR reporting would not occur into EudraVigilance and reporting would only be in a PBRER?

Line 871 We suggest adding 'and organisation data collections' after non-interventional post-authorisation studies.

Lines 882-3 We assume section B refers to a scenario where MAH is the sponsor including contractual agreements in investigator initiated trials?

Lines 890-5 It is difficult to distinguish difference between Sections E and F. Does Section E refer to a study at the request of a competent authority whereas section F refers to voluntary studies?

Lines 903-4 and 906-7 Does 'safety concern' means a signal and/or risk? Or does it refers to 'safety concern' as previously defined under GVP?

Lines 912-14 The use of double negatives makes it difficult to understand

Line 929 More than one method of causality assessment may be applicable depending on the source of the solicited case.

Lines 948-952 Why direct comments to organisations who are unlikely to read this module? What about when MAH is informed of cases even if there is no contract in place? Trying to verify that cases have been expedited by the academic sponsor may be tricky within current timelines.

Line 966 What should HCPs report on the CRF. All AEs in a non-observational study? Or just ADRs? Who should do the collecting?

Line 976 Should this be an ADR or an AE with a fatal outcome rather than just an outcome?

Line 1011-1013 What about outside the EU where requirements for compassionate use may not be specified? Should the MAH apply EU standards globally?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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
EFPIA [redacted]

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).

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	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.

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	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.

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	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 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

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	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.

2. 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')*
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.

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')*
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**:

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')*
		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 occurrence and 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."

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')*
		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."

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')*
		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.

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')*
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,

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')*
		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"

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')*
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.

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')*
		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

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')*
		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.

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')*
		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 Agency pursuant 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.

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')*
		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.

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')*
		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:

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')*
		• 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).

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')*
		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

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')*
		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

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')*
		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.

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')*
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

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')*
		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):

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')*
		"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)**

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')*
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**
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:

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')*
		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

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')*
		• 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"…

3. 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')*
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

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')*
		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 rationale
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 reactions,"
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

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')*
		medicine ~~**(ISCR)**~~ **(ICSR)**" **Ensure that references to "ICSR" are appropriately referenced throughout the document.**

4. 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')*
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

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')*
		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,..

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 OCT 2016

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

Comments from:

Name of organisation or individual
EUCROF- Pharmacovigilance Working Group

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).

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	None

2. 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')*
Comment 33 on page 27		**Comment**: "For combined study designs based on primary and secondary data collection, the same requirements as for studies with primary data collection should be followed". This is a quite important comment deserving more room for clarification in body text and even a specific chapter such as c. ***Non-interventional post-authorisation studies based on combined primary and secondary data collection.*** Frequent interpretation in such cases (e.g. combination of a chart review phase and a prospective phase with patient follow-up) is that the protocol should not mandatorily solicit collection and reporting (or notification) of cases discovered in medical records or databases, contrarily to the prospective primary data collection. As written, the comment seems to require systematic solicited collection/reporting for both phases. Could you please clarify? **Proposed change** (if any): Not applicable
Lines 240 and 243		**Comment**: Is this change only a modification in wording or is there a significant change in the terms "off label use" and "misuse"? If the latter is true, could you please clarify what is now considered as "use not in accordance with the terms of marketing authorisation"? **Proposed change (if any)**: Not applicable
Line 347 and footnote 6		**Comment:** The link to the IME list is incorrect/broken. This part of Eudravigilance has been decommissioned. **Proposed change (if any)**: Not applicable
Lines 358-368		**Comment:** To provide some examples of codes used for nullflavors would help understanding of this section.

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')*
		Proposed change: "Nullflavors are a collection of codes specifying why a valid value is not present in an ICSR. This refers to instances, where for example a proper value is applicable, but not known (code UNK, e.g. age of the patient), or the value is masked i.e. information is available to a sender of an ICSR but cannot be provided due to security, privacy or other reasons (code MSK, e.g. date of birth of the patient). ICH ICSR uses Nullflavour code sets from the HL7 Messaging Standard primarily to classify the set of source data situations that may give rise to a missing value. HL7 code set includes NI, NA, UNK, ASKO, NAV, NASK, MSK, OTH. For examples how a Nullflavors can be used to code values in the ICSR, refer to chapter 3.3.6. of the ICH Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) E2B(R3) Data Elements and Message Specification, Version 5.01, 12 April 20137. Additional EU guidance on the use of the Nullflavor in some specific situations is also provided in chapter I.C.3.7. of the EU Individual Case Safety Report (ICSR) Implementation Guide8."
Lines 602-605		**Comment:** Primary source information may become anonymised in all kinds of reports, especially when the primary source is a physician or a consumer. Why is there a reference to this possibility specifically "for individual 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 747, 752, 766, 793, 981		**Comment**: The use of the terms "submitted", "reported" and "notified" sounds not homogeneous thus ambiguous all over the Module. Whereas several "reported" have been changed for "submitted" we can still find either the combination of the 2 words in the same paragraph, or the use of "notification" for "reporting" and vice versa.

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')*
		Definitions for the 3 terms and at least homogeneous/consistent use of these terms all over in the guidance would be useful. • Submission = does it necessarily mean the sending of an ICSR to competent authorities? • Reporting or Notifying = sending of ICSR to a "notified recipient"? Is this similar to notifying an ICSR as the 2 words seem to be used indifferently? • Is it correct to say for instance in a study protocol: suspected ADRs should be **reported (or notified?)** to the Safety Unit of the study sponsor (the recipient). The notified recipient will triage and **submit** valid ICSRs to competent authorities as appropriate? Examples of inconsistencies or ambiguous wording include: • line 766 VI.B.7. Reporting (better to use submission instead?) of individual case safety reports (ICSRs): Only valid ICSRs (see VI.B.2.) should be submitted. The clock for the reporting (why not submission?) of a valid ICSR etc • line 793: VI.B.7.1. Reporting (or submission?) time frames: In general, the reporting (or submission?) of serious valid ICSRs is required as soon as possible, but in no case later than 15 calendar days after initial receipt of the information… • line 747: The requirement to submit these reports of lack of efficacy does not apply when the notification (or reporting?) occurred in the frame of a non-interventional efficacy study • line 752: Clinical judgement should be used when considering if other cases of lack of therapeutic efficacy qualify for reporting (or submission?) • line 981: For these particular situations, the rational for not reporting (or submitting?) as ICSRs certain adverse reactions with fatal outcomes should be clearly described in the protocol. **Proposed change (if any)**: Not applicable
Line 966-967		**Comment**: "Information on all adverse events should be collected from healthcare professionals or consumers in the course…". Does "collected" also mean that all AEs should be available in the safety (PV) database or is it sufficient to • record all collected AEs in the clinical database • record all collected ADRs in the safety (PV) database Reading line 1096-1098 (stating that MAH should collect all 'suspected adverse reactions') one could argue that it should not be necessary to add unrelated AEs from non-interventional studies to the safety (PV) database.

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')*
		Proposed change (if any): Not applicable
Lines 996		**Comment**: It would be clearer to precise the MAH in charge of the summarization. **Proposed change:** "When made aware of them, these reports should also be summarised by the marketing authorisation holder sponsoring the study in the relevant study reports"
Lines 1211-1212		**Comment**: Does the term "aggregated data analyses" mean something different to "aggregated data"? It could also be clarified that the term "publicly available databases" refers to both the aggregated data and the line listings. Furthermore, could you clarify whether, single cases originating from a publicly available database, but not presented in the form of aggregated data or line listings, qualify for reporting? **Proposed change (if any):** d. which presents aggregated data ~~analysis~~ or line listings from publicly available databases, e.g. poison control centres,
Lines 1213-1214		**Comment:** It is not clear whether point e. includes a summary of the results of one single study or it describes only the articles summarising the results of multiple previously published studies. **Proposed change (if any):** e. which summarises results from post-authorisation study(ies) or literature reviews
Lines 1215-1217		**Comment**: What number of patients is considered a group of patients? Any number greater than one (1)? For example, are two (2) patients considered a group?

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')*
		Proposed change (if any): Not applicable
Lines 2266, 2274 and 2282.		**Comment**: Validity and follow up information can be requested and retrieved by sources other than the primary source. However, in tables VI.2, VI.3 and VI.4, only the "primary source" is used as a possible source of information regarding the case validity and follow up information. Please confirm that the term "primary source" is intentionally used in these tables and please provide explanation why this is so. **Proposed change (if any):** Not applicable
Lines 2714-2717		**Comment:** Some of the examples provided are inconsistent in applying the qualifying descriptors of gender. E.g., Example #8 Vs #15. Example #8 describes a scenario when a patient gender was assumed based on the type of drug administered: an oral contraceptive thus a female patient. On the other hand, as stated in Example #15, 50 patients that developed ovarian cancer cannot be considered as female patients and thus are lacking patient's qualifying descriptor (gender). Could you please explain the underlying difference that allows validating the case in the example 8 and not validating it in the example 15? Moreover, the assumption made in the example 8 might not hold true if a drug was used not in accordance with the terms of marketing authorisation (by male patient). **Proposed change (if any)**: Not applicable
Line 2716 – Example 9		**Comment**: Forwarding of contact information of reporters between companies is not a common practice. In case Company A did not forward the contact information of the reporter to Company B, would this case be assessed as non valid?

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')*
		Proposed change (if any): Not applicable
Line 2716 – Examples 11		**Comment**: In case an employee of the company of Drug Y identified the article, would the employee be considered as a reporter and therefore this would be assessed as a valid case? **Proposed change (if any)**: Not applicable
Line 2716 – Examples 11 and 13		**Comment**: It is not clear to us how examples 11 and 13 differ from one another: Example 11 describes a scenario that a reader of an article for which no authors are listed, can be accepted as an identifiable reporter. On the other hand, as stated in Example 13, a pharmacist reporting safety information that has been reported to him by another reporter, cannot be considered as an identifiable reporter, as this case refers to second hand information. Could you please clarify the difference? **Proposed change (if any)**: Not applicable

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14th of October 2016

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

Comments from:

Name of organisation or individual
Europharm

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	
	NA	

2. 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')*
498-507		**Comment:** Please clarify "However, if the reporter does not wish to provide contact details, the ICSR should still be considered as valid, providing the organisation who was informed of the case was able to confirm it directly with the reporter." Which should be the procedure(s) taken by organisations to demonstrate they are able to confirm the case directly with the reporter? **Proposed change (if any):** The text should be more clear about this topic.
1124-1127		**Comment:** We suggest the GVP should be more detailed regarding product combinations. It is clear that MAH with medicinal product combinations shall report ADRs related to at least one of the products of the combination. Nevertheless nothing is said regarding the opposite: if a MAH as a single product that also exists as a combination in the market, should this MAH report literature ADR reports for a combination product that includes its active substance? **Proposed change (if any):** We suggest clarification and the inclusion of examples for both situations.
602-605		**Comment:** This example clarifies follow-up of a case where, potentially, there is a missing element, the identifiable reporter (anonymous reporting). Should MAH report the initial case expeditly or only keep record of the case? **Proposed change (if any):** Please clarify, since without an identifiable report this is by definition an invalid case.

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')*
437-441		Comment: This sentence is redundant: "first publication author should be considered as the primary source as well as the primary source for regulatory purposes". From our understanding there is only one primary source to consider. Proposed change (if any): "…first publication author should be always considered as the primary source. The co-authors should not be reflected as part of the primary source information".

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

Name of organisation or individual

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*).*

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
FARMAINDUSTRIA	Line 362: ICH ICSR uses Nullflavour code sets from the HL7 Please specify what ICH is the concerned one.
FARMAINDUSTRIA	Lines 395-397: Comment. The sentence: "It does not derive from a study or any organised data collection systems where adverse events reporting is actively sought, as defined in VI.B.1.2." might lead to think that solicited reports are only those where adverse event reporting is actively sought. However definitions in section VI.B.1.2. do not make any references to actively seeking adverse events. Adverse event collection is an important part of any patient support program or market research activity however it is not the primary goal. The key for categorizing reports as solicited, as per lines 473-479, is whether they originate from organised data collection systems and not whether adverse events are sought. Proposed change (if any): It does not derive from a study or any organised data collection systems ~~where adverse events reporting is actively sought~~, as defined in VI.B.1.2.
FARMAINDUSTRIA	Lines 418-428 VI.B.1.1.2 Literature reports: No reference about MLM Service is made in this section. A reference about MLM Service could be included in this section.
FARMAINDUSTRIA	Lines 466-467 Comment: In relation to cases from the internet or digital media, the identifiability of the reporter refers to the possibility of verification of the existence of a real person What data could be considered as data that allows the verification of the existence of a real person?

Stakeholder number *(To be completed by the Agency)*	General comment
	Could a nick name be considered as a valid real person?
FARMAINDUSTRIA	Lines 527-533: … primary source has not indicated a possible causal relationship with the suspected medicinal product. For instance a marketing authorisation holder is made aware that a patient was hospitalised or died, without any further information. In this particular situation, medical judgement should always be applied in deciding whether the notified information is an adverse reaction or an event. For example, a report of sudden death would usually need to be considered as a case of suspected… Please, could you inform about how to proceed if a MAH is aware of a hospitalization or of a death and it is not possible to establish a causal relationship?
FARMAINDUSTRIA	Lines 602-605: 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. Don't know exactly what they mean. An example or any reference to the mention situations (local legal requirements o provision that allow for anonymous reporting) would be appreciated.
FARMAINDUSTRIA	Lines 602-605 VI.B.3 Follow-up of reports: Could it be applied for other situations apart from cases related to medications errors that result in harm?
FARMAINDUSTRIA	Lines 1202-1204 VI.C2.2.3.2 Exclusion criteria for the reporting of ICSR published in the scientific literature: a.where ownership of the medicinal product by the marketing authorisation holder can be excluded on the basis of the criteria detailed in VI.C.2.2.: medicinal product name, active substance name, pharmaceutical form, batch number or route of administration; The reference highlighted in yellow is not correct, because it refers to the same section.

Stakeholder number *(To be completed by the Agency)*	General comment
FARMAINDUSTRIA	Lines 2282:point 6.1 Mailbox to update mailbox: MAH.followup@ema.europa.eu Is it correct? There is only one mail box for all Member States?
FARMAINDUSTRIA	Lines 910, 1548, 2060 Related to the reporting rules of CT, for SUSAR occurred only from NIMP for which the Sponsor is not the MAH of the product, who is the responsible to send it to the EVCTM? The Sponsor or the MAH? If the SAE occurred is related only to the NIMP but the event is listed according the reference document (so event does nor fulfil SUSAR criteria), do the MAH have to report to EV post authorization module if became aware of the event (ie sponsor of study send the case to the MAH according the PV agreements)?
FARMAINDUSTRIA	Section "VI. Appendix 8 Examples of assessment of case validity" Comment: In the section "VI. Appendix 8 Examples of assessment of case validity" there are several examples when the initial reporter is a HCP. However, there are no examples on case validity when the only reporter is a consumer. Proposed change (if any): Could you please provide some examples for this situation? For example, we have a case where a 50-year-old male patient has reported hepatitis with simvastatin but, according to local data protection laws, the company has registered neither his name nor address nor phone number. Can it be considered as a valid case?

2. 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')*

Please add more rows if needed.

Dear Sir, Dear Madam,

I am [redacted] and I am working as [redacted] in Galderma.
We are writing to you regarding the draft version of GVP Module VI (Rev 2) "Management and reporting of adverse reactions to medicinal producst", which is currently on public consultation.

We have a question regarding the Annex 8 of GVP Module VI (Rev 2) : Examples of assessment of case validity.
In example 15, the reporter notified that 50 patients experienced ovarian cancer during treatment with drug X. The case is considered as non-valid for the following reason "report describing definite number of patients with no qualifying descriptor available for each patient". As the adverse reaction reported is ovarian cancer, why could we not consider that patients are female and that the case is valid with patient's qualifying descriptor available (gender)?

We have an additional question on the same topic. If we receive a report with 20 patients who are exposed with one of our drug during pregnancy, do we create 20 valid ICSRs as the patients are presumably female (qualifying descriptor available), or 20 invalid cases or one invalid case (in parallel to your example 15 in the Annex 8) ?

Thank you in advance for your help.

Best regards,

[redacted]
[redacted]
Pharmacovigilance – Galderma International

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 October 2016

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

Comments from:

Name of organisation or individual
Gilead Sciences International Ltd

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 number *(To be completed by the Agency)*	General comment

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
232-260	Comment: Can text be added to clarify when such reports should be collected with or without and adverse event and also as stated below, to have more detailed definition to aid consistency and understanding. Proposed change: more detailed definitions and clarity if to be considered with or without an adverse event
238 - 240	Comment: The draft reflection paper on off label use gives specific examples of indication, route of administration, population, and posology. It would be useful to add this detail to Module VI. Proposed change (if any):Add detail to Module VI
247-249	Comment: This is so broad that as requested above, confirmation that it is occupational exposure here an adverse event occurred in the course of one's occupation e.g. rash after exposure to drug. Comment: add confirmation that intention is exposure with an event and provide an example
249 – 250	Comment: It would be useful to include details on how to manage cases of exposure to products during the manufacturing process, rather to exclude this situation altogether. Proposed change (if any):
294-297	Comment: the guidance clarifies that where the drug is ancillary to the device, device regulations apply. Please add text when the device is integral to the drug e.g. prefilled syringes or inhalers and confirm they fall under the PV requirements of 2001/83
310 – 313	Comment: It is stated that the 'primary source for regulatory purposes' identifies the source of the worldwide case unique identification number by defining the country where the case occurred. However, this may not be the same in the scenario where the patient was travelling at the time of the event and the primary reporter country is different to the country of occurrence. Proposed change (if any): Please provide guidance for this scenario.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
310- 315	Comment: When describing the new R3 field for Primary Source for Regulatory Reporting it would be useful to include text describing how this field drives reportability to the EU NCAs. Proposed change (if any): Suggest using wording from the R3 EU IG e.g. this field determines where the case will be reported as a 'domestic' case and where the case will be reported as a 'foreign' case.
318	Comment: The clarification that supporting medical documentation constitutes a medically confirmed case gets lost by being at the end of 325 Proposed change: Move up
408 – 409	Clarity is requested on this bullet point. Does this mean that if one receives a report from a solicited source (e.g. through for example MR or from literature) and then one also receives report from an unsolicited source, the report should be changed to 'spontaneous'? Proposed change (if any):
413-416	Comment: Given the nature of compassionate use, what scenarios are foreseen where safety data is not collected ? Proposed change: Examples requested
501 – associated footnote 15	Please provide clarity on address – if just an organisation is reported, does this constitute an address? Proposed change (if any):
514 to 515	Consider adding further detail to the end of this example to clarify that this is not valid for reporting purposes, but should be databased for signal detection purposes. Proposed change (if any):
574 to 577	Reference "or age group"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed change (if any): Modify to "…patient's age information or age group…" and "…to obtain age information or age group of the patient…"
591	Suggest that primary route of collecting follow-up for initially reported consumer cases is via the HCP. New text suggests that routinely follow-up should be requested from the consumer directly. Please provide clarity as many FU forms in particular targeted questionnaires may not be appropriate to send to consumers. Proposed change (if any):
810- 816	Consider adding expectedness to this list. Proposed change (if any):
910 – 914	Suggest review of wording as it currently could be read that reports related to IMPs are not reportable under Directive 2001/83/EC – Could further clarity be provided on the reporting modalities for NIMPs? Proposed change (if any):
997-1004	Should this section be aligned with GVP Module VIII which is now clearer with respect to collecting AEs from secondary source and not expediting? Proposed change (if any):
1171	Comment: How will The Agency communicate findings from Medical Literature to the MAHs concerned to enable global reporting? Proposed change (if any):

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1180	Comment: It is not clear whether the MAH should be monitoring website for changes to active substances and literature review. Proposed change (if any):
1184	Please add text to clarify that the MAH still reviews the journals /articles for risk management purposes to avoid having to access the detailed guidance for literature
1279	I cannot see these examples in Module 9 – should they be? Proposed change (if any):
1431 – 1441	Could it be made clear in this section or in the scope of the Module that the requirements here and throughout the Modules that relate to Competent Authorities also relate to apply to regional PV centers in those countries where NCAs delegate the ICSR management to such Regional PV centers? Proposed change (if any):
1451 – 1458	It would be useful if further guidance was included on how MAHs will access the ICSR data from Eudravigilance. Proposed change (if any):
1590 – 1592	As the detail on emerging safety issues is now transferred to GVP Module IX it would be useful to reference GVP Module IX in this section. Proposed change (if any):
1675 – page 51 in the table	As Lack of Efficacy is not a code list in R3 G.k.10 r (additional information on drug) should free text field be used to capture this information or only code as MedDRA term?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed change (if any):
1839 – 1850	Suggest adding further detailed examples from section VI.B.7.3 stating that changes to causality, seriousness etc from internal reviews should be submitted as an amendment report, as currently the only example relates to a change in the MedDRA coding of an event. It would also be useful to include in this module the importance of including a clear reason for the amendment. Proposed change (if any):
1908	It would be useful to refer to the exception for the requirement such that no narrative is required for Non Serious cases Proposed change (if any):Add clarification of no narrative for non-serious cases is expected
2186 - 2187	Comment: Reference is made to the provision of compliance reports then row 2187 refers to quality reviews Proposed Change: Please clarify if these are two separate reports and for compliance also add details regarding expectation of responses to the reports and in what timelines.
2266	General comment on the follow-up process map for MAHs – MAH should not be restricted to these. Many MAHs start follow-up processes as soon as they receive a report and do not wait for the report to be submitted to EV so it would not be beneficial to be held to this specific process. Sections 3.3 and 4.1 Guidance on follow up, timing of follow up and number of attempts etc would be useful. The table numbering is not easy to match with the process map as it has no numbering – reading the text in isolation it can be confusing e.g. point 9 states follow up is not required for a valid ISCR. Proposed change (if any): Please add guidance on follow up expectations based on case type. Please can clarification be given about availability to MAHs of follow up if case received initially by the CA who is performing follow up and also confirmation that as a minimum the CA will support the MAH to get follow up for events of interest. VI.4 is confusing and it is unclear

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	in what situations the CA will involve the MAH in follow up requests.
2774 - Table VI.3	Comment: This table applies only to NCAs, but there is a reference to MAH in No. 13. Please clarify. Proposed change (if any):
2274	Clarification needed to show that this process map is for cases received directly by the NCA. E.g. not received via an MAH Proposed change (if any):
2282 - Table VI.4	It should be acknowledged within this process map that the MAH is already following up the case as per its internal processes. General comment on this process is that is seems administratively heavy (email exchange) in particular when MAHs already are required to have robust follow-up processes in place and that if follow-up is received then it will transmitted via E2B. Regarding the due date in step 5.1 – this will be dependent upon whether the MAH is successful in obtaining the follow-up. Step 10.2 seems redundant as follow-up would be submitted via E2B and the NCA will receive the follow-up report if significant. Should the follow-up process for an MAH seeking support for a follow-up from a case received from an NCA when considered important for evaluation purposes be described? Proposed change (if any):
2605	Comment: Refers to Table VI.13 Proposed change (if any): Amend to Table VI.14
2626	Comment: Refers to Table VI.14 Proposed change (if any): Amend to Table VI.15

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
2633 – Table VI.9	Comment: The flow implies the quality check will be a meeting vs. receipt of a quality finings report. Please clarify as if a meeting is not required the process stops but there could still be findings applicable for a CAPA? Proposed change (if any):
2703 – 2713 – VI. App. 7.6	While this Appendix refers to the processes in Module IX, there is no corresponding reference in Module IX to this process – should this be added? Proposed change (if any):
2716 – 2717 – Table VI.23	Comment: Example No.15 in the table refers to patients who developed ovarian cancer; patients' qualifying descriptors available (can presume female), so case should be considered valid. Proposed change (if any): Amend scenario or amend text in 'Validity assessment' column to state 'Valid case'.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

Name of organisation or individual
[redacted] Guild of Healthcare Pharmacists

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).

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	

The Guild of Healthcare Pharmacists (GHP) supports the proposed changes made regarding the legal requirements affecting the collection, data management and reporting of suspected adverse reactions. The GHP also supports the recommendations regarding the reporting of emerging safety issues or of suspected adverse reactions occurring in special situations.

2. 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')*
Lines 206-260		**Comment:** Line numbers 192-193 states that the module does not address the collection, management and reporting of events but although a definition of an 'adverse reaction' is provided in VI.A.2.1 a definition of an 'adverse event' is not provided. **Proposed change**: Provide a definition of an adverse event i.e. An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.
Line 232-233		Comment: We are pleased to see the inclusion of 'medication error and 'falsified medicinal product' Proposed change (if any):
Line 245		**Comment:** We suggest that an FII should be included within the definition of 'abuse' **Proposed change**: The definition of abuse should read " This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product or fabricated or induced illness (FII) or factitious disorder imposed by another person"
Line 512		**Comment:** A full stop is missing in the sentence **Proposed change**: Place a full stop between the words 'descriptors' and 'Furthermore'
Lines 733-734		**Comment:** We suggest supply of e medicine under a patient group direction (PGD)should be included

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')*
		Proposed change: Add supply of a medicine under a PGD is added to the list of examples in brackets
Line 1604		**Comment:** In addition to active substances should this line also include excipients? **Proposed change**: Line 1604 to read "For medicinal products, which contain more than one active substance or excipient"

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 October 2016

Our reference [redacted]

Draft 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
International Plasma Fractionation Association (IPFA) Our reference [redacted]

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).

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)

Comment 1: As mentioned in line 1396, data on interim arrangements are deleted from the present revision of Module VI, whereas some references to these data still remain in the document (discrepancy).

Comment 2: The word "reported" has been replaced by "submitted" in the whole document. It remains in some places.

What about the words "reporting" and "reportable"?

Comment 3: It would be useful to add the number of the step in the logigramme in order to clarify it.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
251-252 Definition	Medication error Comment: The unintended failure could happen at different steps of prescribing, dispensing or administering the drug, as in line with the definition reported in "Good practice guide on recording, coding, reporting and assessment of medication errors" (EMA/762563/2014) dated 23/Oct/2015, please add the definition. Proposed change (if any): This is an unintended failure in the drug treatment process (at different steps of prescribing, dispensing or administering the drug) that leads to, or has the potential to lead to harm to the patient2.
253	Falsified medicinal product Comment: Is there a difference with a counterfeit drug? If yes, could you provide the definition for "Counterfeit medicinal product"?
508-515	One single identifiable (footnote 12) patient characterised by at least one of the following qualifying descriptors: initials, identification number, date of birth, age, age group or gender. The information should be as complete as possible (footnote 14). An ICSR should not be considered valid for reporting unless information is available for at least one of the patient qualifying descriptors. 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. Comment: See appendix 8, examples N° 6/7: In those examples, even if we do not have initials, gender, date of birth or age group, identification number, it is well known that there is a single patient who presented an adverse reaction. Patients, even if not identifiable by demographic data, can be identified by their medical history, adverse reaction, etc. By precautionary measure, it seems important to

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	consider those cases as valid. How about death cases, should we consider them as not valid for reporting?
602-605	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. Comment: Can you clarify why performing follow-up activities is not possible only in this situation and not in other situations?
805-808	Report nullification Comment: The cross reference VI.C.6.2.2.10 refers to "what to take into account for data protection laws" chapter (1874-1891) and not to nullification of cases. Proposed change (if any): Please provide the correct cross reference (VI.C.6.2.2.9).
1069- 1073	Comment: Do you mean medication error? Proposed change (if any): Member states shall ensure that the reports of suspected adverse reactions arising from a medication error associated with the use of a medicinal product that are brought to their attention are made available to the Eudravigilance database and to any authorities, bodies, organisations and/or institutions, responsible for patient safety within that member state.
1199+1200	Exclusion criteria for the reporting of ICSRs published in the scientific literature, point f: suspected ADR which occur in a group of patients with a designated medicinal product and individual patients cannot be identified for creating valid case reports. Comment: VI.C.2.2.3.2. Should the term "reporting" in the title and in the first sentence be replaced by submission? See general comments

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1235-1236	Comment: It is mentioned "When a report of suspected adverse reactions is associated with a suspected or confirmed falsified medicinal product (see GVP Annex I) or ...." Please confirm to which definition of GVP Annex I the cross reference is made (there is no definition of falsified product in GVP Annex I). Proposed change (if any): /
1248-1253	Comment: The data related to vaccines is mentioned twice. Proposed change (if any): For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product ~~(including vaccines)~~ should be considered as a serious adverse reaction and such cases should be submitted within 15 days in accordance with the requirements outlined in VI.C.4. VI.A.2.4.). This also applies to vaccines. Electronic reporting recommendations provided in VI.C.6.2.3.6. should be followed.
1279	Comment: 1. As mentioned in lines 1590-1594 (section VI.C.6.2.2. Preparation of individual case safety reports), an emerging safety issue should be notified to the competent authorities of the Member States where the medicinal product is authorised and to the Agency in addition to the reporting requirements related to ICSRs. This does not appear in the present section "VI.C.2.2.6. Emerging safety issues". 2. There is no definition of Emerging Safety Issues in GVP Annex I. Proposed change (if any):/.
1280-1281	Comment: Emerging safety issues should be immediately notified in writing to the competent authorities, although it is not with the format of valid ICSRs. 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 related to the ICSRs, even though they may lead to changes in the known risk-benefit balance of a medicinal

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	product and/or impact on public health.
1459-1461	Comment: There is no sub-section VI.C.5.2. Proposed change (if any): Please combine titles VI.C.5 and VI.C.5.1.
1577-1583	Comment: A reference is made to the "the narrative section for serious cases". As mentioned in line 1396, data on interim arrangements are deleted from the present revision of Module VI. As valid non-serious should also be submitted, is the narrative of valid non-serious case concerned by the text mentioned in lines 1577-1583 ? Proposed change (if any): /
1675	Comment: / Proposed change (if any): The following applies in line with ICH-E2B to capture this information, if available:
1708-1710	A case narrative shall be provided, where possible, for all cases with the exception of non-serious cases. Comment: As mentioned in line 1396, data on interim arrangements are deleted from the present revision of Module VI. As valid non-serious should also be submitted, should the narrative of valid non-serious cases be also provided?
1728-1731	Comment: As mentioned in line 1396, data on interim arrangements are deleted from the present revision of Module VI. Proposed change (if any): ~~During the interim arrangements (see VI.C.4.1.), t~~The case narratives included in the ICSRs submitted to the competent authorities in Member States by marketing authorisation holders, should not be modified or deleted when the ICSRs are forwarded to the EudraVigilance database by the competent authorities.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1763	Comment: As said line 1759-1759, "if it is not possible to provide information on tests and tests results…" Proposed change (if any): In line with ICH-E2B the following applies, if information on tests and tests results are available:
1794-1795	Comment: Typing error Proposed change (if any): Significant new information relates to, for example, a new suspected adverse reactions
1803-1805	When new administrative information that could impact on the case management is available, a new version of an ICSR should be submitted. Comment: Could you clarify how this new version should be submitted ? Is it a FU report or an amendement report or other?
1899-1901	The foot note 58 mentions "In practice, the original verbatim text reported by the primary source in an official language of the Union other than English should be included in the ICSR, if it is requested by the Member State where the reaction occurred or by the Agency". Comment: Could this sentence be added in the section as a full text (and not as a foot note)?
1908	Comment: Please refer to footnote 58 Proposed change (if any): In line with ICH-E2B the following applies, if it is requested by the Member State where the reaction occurred or by the Agency:
1947	"ICH-E2B(R3): Section H.5.r 'Case Summary and Reporter's Comments in Native Language (repeat as necessary)' should be used to provide the medical summary for the entire case and where both parents are the source of the suspected drug(s), the father's characteristics should be also reflected here."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Comment: Why should the case summary and reporter's comments provided in native language? With reference to the foot note 58, it should be provided only if requested by the Member State where the reaction occurred or by the Agency.
1998	Comment: Typing error Proposed change (if any): ICH-E2B(R3): This is to indicate that the medicine may have been associated with XXX as defined in chapter VI.A.2.1.2.a.
2214-2215	Comment: As mentioned in line 1396, data on interim arrangements are deleted from the present revision of Module VI. Proposed change (if any): ~~This applies as well for the interim arrangement period, where based on the reporting requirement detailed in VI.C.4.1.~~
2265	Comment: Please clarify the logigramme Proposed change (if any): add the number of the step in the logigramme
2270	Comment: Please clarify the logigramme Proposed change (if any): add the number of the step in the logigramme
2280	Comment: Please clarify the logigramme Proposed change (if any): add the number of the step in the logigramme
2289	Comment: Please clarify the logigramme

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed change (if any): add the number of the step in the logigramme
2627 (8)	However, the patient … other suspect drug. It is recommended that the initial sender informs the other marketing authorisation holder about this case: Comment: when the case should not be nullified when it is confirmed that the patient did not receive the marketing authorisation holder's suspect drug. what about cases with unknown brand name?
2634	Comment: Please report the numbers used in the logigramme' explanation in the logigramme itself
2640/Page 135 (step 1)	Comment: Typing error Proposed change (if any): Step column: Receive reports of suspected ~~drug~~ adverse drug reactions(s) from NCAs and MAHs Description column: ICSRs are received in electronic format in EudraVigilance from sender organisations with reporting obligations of suspected adverse drug reactions related to medicines authorised in the EEA
P2640/age 136 Step 3.1	Comment: The responsible organisation is not specified
2640/Page 136 Step 5	Comment: Is the meeting required with EMA?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
2640/Page 137 Step 6.	Comment: The responsible organisation is not specified
2640/Page 138 Step 8.3.	Comment: Clarify that part of the sentence "monitor the implementation the agreed corrective measures". What is the difference with step 8.4? And Typing error: monitor the implementation of the agreed corrective measures"
2640/Page 138 Step 8.4.	Comment: Does it mean that any corrections (even if not medically relevant) performed in the case upon the quality review performed by EMA will need to be resubmitted to EV? If yes, to be specified in the logigramme If no, how EMA will check that corrective measures were implemented?
2650/2651	Comment: There should be a link between "Local PhV database" and "Sender to update/nullify ICSR and report to EV. As a matter of fact, before to submit the case to EV, the sender has to update its PhV database. Proposed change (if any): To delete the box "Local PhV database".
2654/Page 143 Step 4.2	Comment: no responsible organisation specified Proposed change (if any): Add EMA
2665/Page 147 N°7	Comment: Proposed change (if any): Before the line "If Yes", add "Cases are confirmed to be duplicates"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Add the responsible organisation
2665/Page 148 N° 8.1	Comment: Wrong responsible organisation Proposed change (if any): It should be EMA and not "Sender organisations"
2679 N°4.1	Comment: Proposed change (if any): The MAH identifies the duplicates sent to Eudravigilance as part of their duplicate management process
2697	Comment: Can you provide examples of situations of "merge" case where nullification of duplicates could not be performed?
2697	Comment: Typing error Proposed change (if any): Box "Detection of duplicates in owner PV database"
2701/Page 157 Step 5.2.1	Comment: Can you provide some examples where duplicates could not be nullified if a master case was created?
2716/Page 162: N° 6/7	Comment: In those examples, even if we do not have initials, gender, date of birth or age group, identification number; it is well known that there is a single patient who presented an adverse reaction. Patients, even if not identifiable by demographic data, can be identified by their medical history, adverse reaction, etc. By precautionary measure, it seems important to consider those cases as valid.
2717/Page 164 N° 13	Comment: In line 498, it was not specified that cases are considered valid only if the reporter is the one who had the information from the patient. In the example provided, the case was reported to the pharmacist by a neighbour but, at hospital, we may often have cases reported by the pharmacist who had the information through a physician. By precautionary measure, it seems important to consider cases received from second hand information as valid.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7-10-2016

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

Comments from:

Name of organisation or individual
Netherlands Pharmacovigilance Centre Lareb [redacted]

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 number *(To be completed by the Agency)*	General comment	

2. 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')*
P 15 VI.B.2 line 564-566		Comment: 'ICSR seriousness criterium should not be downgraded from serious to non-serious' This applies to ICSRs from healthcare professionals, but not to all consumer reports. Some consumers do not read or understood the CIOMS criteria correctly or they report that they fear for a serious event but do not have this reaction. Some examples: - consumer reports a high cholesterol as ADR and mentions this as CIOMS lifethreatening, but no treatment occurred for this event - consumer mentions that he was ill and unable to go to work for three days but added CIOMS disabling to this ICSR. - consumer doesn't understood the reporting form and marks all CIOMS criteria, also congintal anomaly. ADR concerns cough. Proposed change (if any): In this cases the assessor must have the opportunity to downgrade such a ICSR, when from the ICSR becomes clear there is no evident reason for seriousness.
P18 VI.B.6.1 line 663		Comment: 'embryo or foetus may have been exposed to medicinal products…. via semen following paternal exposure' can be read as though paternal influence is restricted to an existing pregnancy, through exposure of the embryo/fetus via his semen. However paternal influence is not restricted to an existing pregnancy. Paternal exposure before conception can affect (the quality) of his semen, which can be of influence on the pregnancy later on. For instance by increasing the risk of a spontaneous abortion. Proposed change (if any): On page 62 this is better defined. Please bring the text on pag 18 in line with text on page 62.
P34 VI.C.2.2.3.2 line 1215-1216		Comment: '…..and individual patients cannot be identified for creating valid reports' It is not clear to whom the patients must be identifiable: The author(s) of the paper, the treating physician or the

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')*
		organization receiving the ICSR (NCA or MAH). Further clarification is needed. Proposed change (if any):
P 46 VI.C.6.2.2.2 line 1602-1603		Comment: 'The characterization of…. Is based on the information provided by primary source.' In most ICSRs, this is the case. However, in some situations the assessor wants to change the characterization of the suspect, interacting or concomitant drugs, f.e. in situations: - primary source is indication all drugs as suspect, but in the narrative it becomes clear that only one drug is suspect - some drugs are reported as suspect and others as interactions. This is not in line with meddra points to considere, where there should be at least 2 interacting drugs Proposed change (if any): In this cases the characterization of the drugs should be adapted by the assessor with a comment in the senders comment. Please adjust this in P 46 VI.C.6.2.2.2 line 1602-1603

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 October 2016

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

Comments from:

Name of organisation or individual
CBG-MEB

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*).*

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	It is very useful that regulatory and more technical guidance are combined in one document now.

2. 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')*
564		Comment: Especially with consumer reports that are received via electronic reporting forms, it is noted that the concept of seriousness is not always well understood. Cases are stated to be serious by consumers for situations that are usually considered not to be serious by PhV staff (e.g. patient could not work for 3 days and has selected the disability criterion). Is it also in the very obvious cases not allowed to downgrade the ICSR to non-serious? Proposed change (if any):
1373		Comment: Is it correct to say that the E2B data element 'does this case fulfil the local criteria for an expedited report' can be set to 'Yes' (for R2) or 'True' (for R3) for all serious and non-serious cases? Are there situations where ICSRs will be submitted with other values for this data-element? Proposed change (if any):
1602		Comment: similar comment for line 564: we have experienced that the reporters choice for 'suspect' or 'interacting' can not always be relied on when reports are received from consumers via electronic forms. For obvious cases it should be possible to change this. Proposed change (if any):
1748		Comment: It may not be clear to every reader what is meant by "different sources" and "different methods of assessment". Please clarify, or alternatively, make more explicit reference to ICH E2B guidance here.

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')*
2274 (no 3.2)		Comment: replace 'MAH' with 'NCA' Proposed change: "… if time permits and follow-up information can be obtained and processed within the initial reporting timeframes, the ~~MAH~~ *NCA* is not required to report the initial and the follow-up report separately "
2282 (no 5.1)		Comment: In the absence of defined criteria we suggest to use the word 'justification' instead here for requests to involve MAH in follow-up.
2417		Comment: Could you please clarify if separate ICSRs should be created based on a summary table in a publication (e.g. where the table refers to 80 adult males, should this lead to 80 separate ICSRs)?

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14-Oct-2016

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

Comments from:

Name of organisation or individual
medac GmbH

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*).*

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We would like to comment on paragraphs: VI.C.2.2.3.2 Exclusion criteria for the reporting of ICSRs published in the scientific literature This paragraph has been topic for discussion in our company, in particular sections c, d, e and f, which we would like to comment/question on: Section C: Could you please give an explanation / an example what "analysis from a competent authority database within the EU" are? Section D: Within one of the MLM Webinars participants and speaker were discussing about the meaning of „publicly available databases". We came to the conclusion that publicly available databases are also Embase and Medline. In the current revision you name "poison control centers" as publicly available database. Literature articles from poison control centers are rather rare compared to the databases mentioned before. Is it possible to name Medline or Embase as examples for publicly available databases? Section E AND F *"which summarises results from post-authorisation studies or literature reviews"* *"which describes suspected adverse reactions, which occur in a group of patients with a designated medicinal product and individual patients cannot be identified for creating valid case reports"* We agree that data from review articles are secondary data and should not be processed twice. However, it is difficult to interpret what a "summary of results" is. Is it already the listing of data in a table or line listing (like pointed out in previous GVP VI version)? Or do you mean that a "summary" has to be a setting in which data cannot be attributed to single patient data, e.g. "20% of the patients developed neutropenia after administration of drug xy"? As stated in section F, an ICSR should be generated as soon as patient identifiers are given. Sometimes, identifiers are already given by the cohort of patients being treated (e.g. breast cancer patients, ergo: female patients) and it would be technically possible to generate ICSRs. However, further data are usually rarely available and in most of the cases receive of follow-up information is not possible. A valid causality assessment is rarely possible and thus the impact of ICSR processing of these kind of articles on patient's safety is questionable. The aim of articles on post-authorisation studies or on groups of patients is to identify and quantify a safety hazard or risk in a specific patient population, not to focus on adverse drug reactions in single patients. We propose that it is rather useful to discuss those articles in complete at other parts of pharmacovigilance system, e.g. PSURs or signal management

Stakeholder number *(To be completed by the Agency)*	General comment
	processes. Regarding ICSR processing from literature articles we propose that it is rather useful to focus on "real" case reports than on aggregated patient data in post-authorisation studies/group of patiens. VI.C.2.2.3.1 Monitoring of medical literature by the European Medicines Agency The paragraph describes the medical literature monitoring by the EMA and explicitly states that duplicate reporting shall be avoided by MAHs. However currently there is no possibility for MAHs to perform a duplicate check within the system provided by the EMA. As duplicate management is an essential part of pharmacovigilance we would propose to add a possibility for MAHs to perform duplicate checks within the MLM system (e.g. by including the "Literature Ref" field into the search field selection of the EVWEB WebTrader for MLM Reports). VI.C.3. Reporting time frames The paragraph describes the data element A.1.9 'Does this case fulfil local criteria for an expedited report?' which should be used to provide a mechanism to the sender to indicate whether the case fulfils the local expedited requirements. However the completion of this data element is not clearly described. According to our understanding there are 2 possibilities how to complete this E2B field: • The data element shall be completed with 'yes' when all criteria for a valid case are fulfilled and the MAH submits the case report to authorities according to EU requirements. • The data element shall be completed with 'yes' when all criteria for a valid case to be reported are fulfilled independently whether the MAH actually performs the submission to authorities (e.g. case reports in which no reporting is required since the reports are received from an authority). With the first possibility we discovered the following difficulty: in a case report submitted by an authority to a MAH this field is completed with 'yes' in the received XML file since the local expedited requirements were fulfilled. When the case is uploaded into the MAHs database and the case will be electronically retransmitted to a non-NCA receiver, this data element will still be completed with "yes" since during electronic retransmission the case should not in principle be omitted or changed. However, no reporting to authority has been performed by the resubmitting MAH. As there are two possibilities how to interpret the meaning of this data element could you please further explain what is meant by "the case fulfils local expedited requirements"?

2. 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')*
		Comment: Proposed change (if any):
		Comment: Proposed change (if any):
		Comment: Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016

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

Comments from:

Name of organisation or individual
Medicines for Europe Contact: [redacted]

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).

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Medicines for Europe welcomes this opportunity to provide comments. The modifications made in the revised module are clearly a step in the right direction. We welcome the clarifications on some of the topics which are much appreciated. However, having the mind the EudraVigilance (EV) system with enhanced functionalities will be launched end of 2017 - which is approximately the same time as this module will become valid – we believe the revision misses opportunity on more pragmatic and comprehensive guidance on topics that will play more significant role the near future, e.g. patient support programme (PSP), market research, off-label use and social media.
	The update on the electronic reporting modalities of ICSRs under the new ICH-E2B(R3) format brings some technical note to the document, nevertheless we support Agency's efforts to have a comprehensive overview gathered in one document.
	In addition, the use of '**special situation'** is not consistent throughout the module and might be misleading in its interpretation. Clarification and clear and consistent use would be welcome. In section VI.A: Definition mentioned: 1. Overdose 2. off-label use 3. misuse 4. abuse 5. occupational exposure 6. medication error 7. falsified medicinal product In section VI.B.6. Special situations mentioned: 1. Pregnancy 2. breastfeeding 3. Paediatric

Stakeholder number *(To be completed by the Agency)*	General comment
	4. elderly population 5. overdose 6. abuse 7. off-label use 8. misuse 9. medication error 10. Occupational exposure 11. Lack of therapeutic efficacy In section VI.C.6.2.3. Special situations 1. Pregnancy 2. Breastfeeding 3. scientific literature 4. overdose 5. abuse 6. off-label use 7. misuse 8. medication error 9. occupational exposure 10. Lack of therapeutic efficacy 11. quality defect 12. falsified medicinal 13. transmission via a medicinal product of an infectious agent

2. 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')*
Line 199		Comment: It should be clarified that section B is also relevant in Member states where the actual collection and submission is not done by the Member state but by a delegated organisation. A specific example in this is the Lareb in the Netherlands. Proposed change: Clarify that for these organisations section B is relevant in regard to Follow up of case reports for age, batch number and other obligations. Reference should be made to VI.B.3
Line 238		Comment: Although we do understand the necessity of reporting on off label use which could be seen as relevant with regard to patient safety there are a lot of situations where off label use is intended off label use and seen as best medical practice. Opioids dosing in palliative care, eye/ear drops with antibiotics instead of ointments/creams to be used topical etc. etc. There are numerous examples. These cases or off label use are not relevant in terms of patient safety and are generating confusion and unneeded workload. Medicines for Europe would encourage a discussion on the definition of off label use in the interest of patient safety, resulting in a change of the requirements.
Line 250		Comment: The definition of occupational exposure has changed. In our opinion adverse events caused by exposure to bulk active substance can generate relevant safety information which should be taken into account in the evaluation of the safety profile of the substance. Proposed change: Please delete the added sentence on limitations of occupational exposure.
Line 255		Comment: Clarification would be needed to make sure it is made clear whether it is 'and' or 'or' or 'and/or'. Proposed change: Add "and/or" between the bullet-points.

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')*
Line 332		Comment: Kindly consider to add a clarification if inpatient Hospice and similar (like Rehab) are considered hospitalization Proposed change: Please add to Annex I or this GVP a clarification of the definition.
Line 432		Comment: Literature reports are described under unsolicited reports. However the following sentence "…originating from spontaneous reports or non-interventional post-authorisation studies. "is ambiguous regarding how the case should be handled. Do we have to consider literature cases originating from non - interventional study as solicited report or not
Line 466		Comment: It's unclear whether in reports from digital media if a patient reporting about himself and only his email address is known (identifiable reporter) but no other details as required (no name/age/gender etc.) for the patient to be considered as a valid patient are available –should this report be considered as a valid report? Proposed change: Please consider to add to "VI. Appendix 8 Examples of assessment of case validity" (line 2714) the following example (or another example about patient reporting about himself in social media reports): A Consumer reporting about himself via social media Contact details: No details about the consumer except for his valid email address. Please indicate in the "Validity assessment" if this case is a Valid case
Line 466		Comment: Automated (by search engines) of the internet (digital listening) is regularly used as a tool in market research, in this way records are searched and potentially a huge number of adverse events can be identified without proper event, drug, reporter or patient. This should be excluded from the collecting and follow up responsibilities as long as it is a structured research with a protocol, not directed to specifically to detect safety information.

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')*
		Proposal: add "Digital listening by search engines (automated) in market research should be excluded from the collecting/follow up responsibilities as long as it is a structured research with a protocol, not directed specifically to detect safety information."
Line 474		Comment: With the increased clarity given in VI.B.1.1.1. with regard to organised data collection systems where adverse events are actively sought, more clarity should also be given in this section on solicited reports. Organised data selection systems like patient support programs where which do not systematically collect AEs, but which do generate regular MAH initiated contact with a patient should be considered solicited. Proposed change: Please add "Organised data selection systems like patient support programs where which do no systematically collect AEs, but which do generate regular MAH initiated contact with a patient should be considered solicited".
Lines 489, 496, 789, 1663, 1775, 1843 etc.		Comment: The "**sent**" and "**submitted**" are used alternately throughout the module without consistency and clarity if the terms differ or not. Similarly, it is not clear on sent (current version) and reported (previous version) difference. The use of 'reported' gave a clear direction it should be reported to Health Authorities, which is not the case any longer. Proposed change: Consider replacing 'sent' by 'report'.
Lines 506-507		Comment: The following sentence is unclear: "All parties providing case information or approached for case information should be identifiable." What is the consequence in term of validity of the case when the initial reporter does not want to identify him/herself but refers in the initial report to another reporter who is identifiable? Or if a duplicate report comes in from a second unidentifiable reporter? Proposed change: Please provide some further clarification.

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')*
Lines 498 and 508		Comment: It is unclear whether the report will be considered as valid if a patient is reporting about himself but his contact details are unknown (he is not a contactable=as a "reporter" he isn't valid) Proposed change: Please consider to add to "VI. Appendix 8 Examples of assessment of case validity" (line 2714) the following example (or another example about patient reporting about himself): Patient 23 years old reporting about himself (no additional information about the patient) Qualification: Consumer Contact details - NON; Name: unknown Please indicate in the "Validity assessment" if this case is a Valid case (the patient is valid but we don't have enough information for this patient to be a valid as a reporter)
Line 508		Comment: According to ICH E2D "One or more of the following *should automatically qualify* a patient as identifiable: age (or age category, e.g., adolescent, adult, elderly), gender, initials, date of birth, name, or patient identification number." This means that E2D also accepts other characteristics as identifiable, but the above are automatically qualified. GVP is now more restrictive *since it limits* the identifiability to the terminology as used in E2D; to age (or age category, e.g., adolescent, adult, elderly), gender, initials, date of birth, name, or patient identification number. Proposal: Consistency with ICE E2D is needed.
Line 514		Comment: The example provided causes more confusion than clarity. There might be several reasons in these example why it is not valid. Proposed change: Please consider deleting or providing a more clear example.

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')*
Line 577		Comment: It should be made clear that the obligations to follow up should also be valid for additional pharmacovigilance activities as for example questionnaires as described in the RMP. Also follow up on batch numbers for biologicals. Those obligations should also be valid for Member states and delegated organisations Proposed change: Add "The provision in ICSRs of follow up information in relation to additional pharmacovigilance activities as questionnaires is important in order to fulfil the RMP obligations. All possible efforts should be made to follow-up on an individual case to obtain the required information of the patient or the HCP, where it is initially not reported by the primary source.
Line 602		Comment: This situation is not limited to medication errors. Proposed change: change the sentence: For individual cases ~~related to medication errors that result in harm~~,
Lines 643-644		Comment: Quality control in data entry is confused with auditing of the data entry. Proposed change: Change into "Correct data entry, including the appropriate use of terminologies, should be monitored by *quality control systemically* ~~quality assurance auditing, either systematically~~ or by regular random evaluation *in quality assurance auditing*
Line 660		Comment: Please consider to add the definition of the special situations to Annex I (definitions)
Lines 663-666		Comment: An exception to the requirement to FU after delivery for exposure to medicinal products during pregnancy should be made for products which are indicated to be used in pregnancy or for which the SPC states use in pregnancy is allowed. An example for this is folic acid, where no FU for pharmacovigilance reasons is needed.

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')*
		Proposed change: Add "There is no requirement to follow up on exposure to a product which is indicated in pregnancy or which is safe to be used in pregnancies according to the SmPC. Spontaneous reported adverse events on negative outcomes however have to be submitted as an ISCR"
Line 707		Comment: Use of a medicinal product in a paediatric or elderly population; This is really not a special situation but a follow up requirement for case Quality. In the terminology having this added under special situations is confusion. A special situation is a situation for which collecting cases might be required also without an adverse event. In the case of paediatric or elderly population there is no requirement to collect other situations only because of the population. Proposed change: We propose to move this section from VI.B.6 to VI.B.3.
Line 781		Comment: clarification to the term 'awareness' should be given. Proposed change: Please add reference VI.App2.7
Line 996		Comment: Those spontaneous reports can only be addressed in the relevant study report when they are reported as happened during a study. An example of a spontaneous report would be a rash due to a non-studied OTC product used during the study. And by coincidence the OTC product would have the same MAH as the MAH conducting the study. To report such an adverse event on a non-studied medicinal product in the study report of a study does not help patient safety and seems to be an requirement causing duplication of efforts without increased patient safety nor efficiency in the operation of the pharmacovigilance network. If these spontaneous cases would be addressed in a CSR it would be limited to the adverse events reported on products which by coincidence has the same MAH, so those listings would be of no value. These reports are assessed and evaluated through the regular pharmacovigilance activities of the MAH.

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')*
		Proposed change: "When made aware ~~of them~~ *of the relation to the study in the report and when the report is of medical/safety significance in relation to the study*, these reports should also be summarised by the marketing authorisation holder in the relevant study reports.
Line 1025		Comment: a specific requirement in this section should be made on the adherence of member states to VI.B.3 Follow up reports including the obligation to follow up on additional pharmacovigilance activities which are required for certain products in the scope of the RMP. This should also be valid for Member states who delegate the collection and submission of ICSRs to third parties.
Line 1279		Comment: the examples of the emerging safety issues are deleted from this module. They are however also not mentioned in module IX. In our opinion these examples are relevant and should be either in module VI or in Module IX
Line 1396		Comment: We understand that the announcement of the functionalities of Eudravigilance is foreseen in the near future. We would propose however to keep an interim solution in case there is a delay in the announcement in order that the clarity which is provided in this module can be used in an earlier stage. Proposed change: Keep interim solutions in order that the module can be finalised and come into effect independent of the Eudravigilance announcement.
Line 1661		Comment: It would be helpful and welcome to add the definition of 'adjuvant' to the module, since it has been added in the section of 'Reporting' but not in the definitions part. Proposed change: Please add the definition of 'adjuvant' to e.g. section VI.A.2.2.
Line 1880		Comment: There is a lot of unclarity with regard to the relevant countries as indicated in this sentence. Can the relevant countries be given?

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')*
Line 2270		Comment: add follow up regarding questionnaires as part of additional pharmacovigilance activities in relation to a substance specific RMP.
Line 2545		Comment: • Examples for the reporting of suspected adverse reactions described in the scientific and medical literature and referring to more than one patient: "A literature article describes suspected adverse reactions that have been experienced by more than one identifiable patient. ICSRs should be created and reported/ submitted for each individual identifiable patient described in the literature article. • Each ICSR should contain all the available information on the case. The cross reference with all the linked ICSRs from this literature article should only be provided in the first case, in the data element ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report'. There is no need to repeat all the cross references in the other ICSRs." Proposed change: • Please consider adding a clarification regarding the meaning of the "first case" – should this be the first case entered? First patient? First submitted case? In some instances some of the cases shouldn't be submitted (for example Non Serious cases) and thus we would link all the cases to the first case that need to be submitted – this will contribute to add the clarification or to change the wording accordingly. • Please consider to adding to the instructions below also that this is applicable for Non-Literature "cluster" cases.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from: Mundipharma Research GmbH & Co.KG

Name of organisation or individual
[redacted]

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*).*

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We thank you for the opportunity to comment on this revised GVP VI version. Overall we find Revision 2 quite improved towards the current first revised version thanks to the use of the standard format tables across the text to outline the differences depending on the use of either ICH-E2B(R2) or ICH-E2B(R3). Please find our overall few specific comments on the following pages, most of which we trust you will find very easy to resolve.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1670-1674	Comment: We agree to the general concept to encode "special situations" as listed in lines 1988ff (Section VI.C.6.2.3.3. Overdose etc.) and 2015ff (Section VI.C.6.2.3.5. Drug taken beyond expiry date etc.) as adverse event and also to the new concept to allocate these to suspect products (this are "d. Additional Information on Drug" - lines 1670. However, as the latter will be new to readers, we kindly suggest to rephrase the text in lines 1670-1674 to • Crossrefer to the AE sections VI.C.6.2.3.3. and Section VI.C.6.2.3.5. • Clarify in the introduction that there are two areas of interest as reflected in the two above mentioned sections. • Recheck the content of the table in line 1675 to match to the breakout into these two areas. • Particularly we found the mention of "drug taken by father" (a specific example for a special situation that does not appear in sections VI.C.6.2.3.3. and Section VI.C.6.2.3.5. and also does not represent a MedDRA LLT in version 19.1 slightly confusing. Proposed change (if any): ~~Often, additional information on the medicine(s) is provided in individual cases, which is important~~ ~~for~~ For the purpose of data analysis and case review it is important to capture various special situations, for example harm in the context of a counterfeit product, overdose, etc. These special situations should be captured both as adverse events and together with the suspect drug product for which the special situation applies. For encoding as adverse events cross-reference is made to sections VI.C.6.2.3.3. (medication error, misuse, abuse, occupational exposure and off label use) ~~taken by father,~~ and Section VI.C.6.2.3.5. (drug taken beyond expiry date, batch and lot tested and found within or not within specifications, ~~batch and lot tested and found not within specifications, medication error, misuse, abuse, occupational exposure and off label use.~~ counterfeit product). For capture in relation to the respective suspect drug product, information is provided in the table below.
1675, ICH-E2B(R3) - section, Second bullet point	Comment: Order of terms not ideal to discriminate between the two areas as outlined in sections VI.C.6.2.3.3. and Section VI.C.6.2.3.5. Proposed change (if any): Data element G.k.10.r 'Additional Information on Drug (coded)' should be completed using one or more of the following values as applicable: Counterfeit, ~~Overdose, Drug taken by father,~~ Drug taken beyond expiry date, Batch and lot tested and found within specifications, Batch and lot tested and found not within specifications, Overdose, Medication error, Misuse, Abuse, Occupational exposure and Off label use. The value(s) should be used where the primary source has made a clear statement related to the

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	additional characteristics of the drug.
1675, ICH-E2B(R3) - section, Text below fifth bullet point	Comment: This comment applies to the following text and the four examples listed underneath which should be coded. Values definition for data element G.k.10.r 'Additional Information on Drug (coded)' Proposed change (if any): The values provided should match MedDRA concepts. • Example: instead of "Counterfeit" state "Product counterfeit" (MedDRA PT). • Instead of "Drug taken beyond expiry date" (which is not a MedDRA LLT) reference to "Expired product" (a MedDRA component part of some LLTs which link to different PTs as appropriate). • MedDRA version 19.1 does not contain "batch" or "specification", so it is not clear how the last two elements should be coded. The other concepts of interest (Overdose, medication error etc.) are missing in this list.
2568	Comment: in the flowchart header which currently reads Business process map - ~~Suspected adverse reaction~~ ICSRs reporting in EU the terms Suspected adverse reaction should not be deleted. Otherwise readers could be misguided to think that negative causality adverse events require expediting. Proposed change (if any): Business process map - Suspected adverse reaction ICSRs reporting in EU
2605	Comment: Link to table number inaccurate. Proposed change (if any): The link should read "…provided in Table VI.14.".
2626	Comment: Link to table number inaccurate. Proposed change (if any): The link should read "…provided in Table VI.15.".

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
2627 (Example 8)	Comment: In the scenario provided (… it is confirmed that the patient did not receive the marketing authorisation holder's suspect drug) the case should be nullified. Justification: The MAH should not "count" a case not referring to his products in his own reports. The update of the GVP modules entails the recommendation to send the case to the MAH affected and that this MAH should create a new case. Therewith the case would be duplicated. Proposed change (if any): Provide the scenario twice: If "MAH 1" with the case where nullification is considered follows the recommendation (send the case to the other MAH who is affected), MAH 1 is allowed to nullify. Otherwise not.
2627 (Example 12)	Comment: The same comment and proposed change as for Example 8 applies. Proposed change (if any): See one line above - Example 8.
2627 (Example 13)	Comment: The case should be nullified if the marketing authorisation holder can demonstrate that the suspected medicinal product has never been supplied or placed on the market in that territory or that the product is not a travel medicine (e.g., anti-malarial medicinal product). Otherwise the request to maintain the case is not in-line with the upfront decision not to create a case in the first place as provided in lines 1120-1123. Proposed change (if any): Provide the scenario twice: If the MAH can demonstrate as outlined above, the MAH is allowed to nullify. Otherwise the case should be maintained.
2714	Comment: Typo in header: "… assesment …" Proposed change (if any): Please change to "… assessment …".
2716, No. 3 in the	Comment: Validity assessment column entry starts with: "Valid case"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
table	Proposed change (if any): "Valid case<u>s</u>". This is because in the example two cases will need to be processed in the safety database.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14-Oct-2016

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

Comments from:

Name of organisation or individual
Otsuka

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 number *(To be completed by the Agency)*	General comment
	Table VI.15, item 8: Suggest clarification: Should the ICSR be resubmitted with the company suspect product still included as well as the other MAHs suspect product?

2. 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')*
362		Typographical error: nullflavor spelt inconsistently on line 362 as the ICH terms are kept in US English in other instances
404		Typographical error: open quotation mark on line 404.
410-412 & 988-989 & 985- 987 Table VI.1 966-968		The proposed language in 410-412 & 988-989 & 985- 987 Table VI.1 and section 966-968 makes it hard to understand what the requirements are with respect to collection of non-fatal AEs from Non-interventional studies with primary data collection. The table VI.1 suggests a "none unless specifically required by the protocol" approach (see the header of the table). Rows 410-412 and 988-989 can be interpreted such that the requirement for collection of specific AEs should be in the protocol ("none unless"). In contrast lines 966-968 indicates a collect all unless there is a due justification in the protocol approach ("all unless").
702-7013		If the GVP P III is not yet available at the time of this module becoming effective guidance how to handle the interim situation would be helpful. Similar for other future documents mentioned in this draft.
893		Considering the non-interventional nature of these studies, how relevant is it to distinguish between "conducted in accordance with the terms of the marketing authorisation of the medicinal product" (section F) and Section E? Can this be simplified?
1532		Formatting error: line 1532, the E2B R2 line is in the header of the table.
1105-1106 1129-1130		Comment: duplicate statement provided in lines 1105-1106 and 1129-1130. On this aspect further guidance is needed for the situation where the partner holds the safety data base whether it is acceptable that the point of access for the safety base is different from that of the safety database of the MAH itself Proposed change (if any): Consider an over-arching statement regarding the single point of data access regardless of the type.
2150-2153		Comment: duplicate statement provided in lines 2150 and 2153.

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')*
		Proposed change (if any): Consider removing addition on 2153.
2150 2156-2157 2158-2159		Comment: consider consolidating the language from 2156-2157 and 2158-2159. Also, change to complete the item bulleted at 2150. Proposed change (if any): the collaboration between marketing authorization holders and the member states with the Agency in the detection of duplicates of suspected adverse reaction reports [DIR Art 107(5) and DIR Art 107a (3)].

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016

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

Comments from:

Name of organisation or individual
PHARMIG – Association of the Austrian pharmaceutical industry

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 number *(To be completed by the Agency)*	General comment
	PHARMIG, the association of the Austrian pharmaceutical industry, welcomes the opportunity to comment on the draft Rev. 2 of GVP Module VI.
	It is very much acknowledged that the term used submission versus reporting contributes to a further clarification of the Module.

2. 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')*
405-407		Comment: For more detailed clarification and consistency throughout the document the sentence should be amended Proposed change (if any): Reports of suspected adverse reactions, which are not related to any organised data collection systems in which adverse event information is actively sought and which are notified through medical enquiry/product information services or which are consequent of the distribution of information materials including additional Risk Minimisation Programs;
413-415		Comment: For more detailed clarification and consistency throughout the document the sentence should be amended Proposed change (if any): Reports of suspected adverse reactions originating from compassionate use or named patient use conducted in a country where the active ~~collection~~ sought 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).
473- 477		Comment: For more detailed clarification and consistency throughout the document the sentence should be amended as registries are falling under non-interventional studies as they are a study designs see GVP Module VIII. If a registry is a disease registry no linked information to a medicinal product is done and would therefore not fall under the Drug act. Proposed change (if any): As defined in ICH-E2D (see GVP Annex IV), solicited reports of suspected adverse reactions are those derived from organised data collection systems, which include clinical trials, non-interventional studies including registries, post-approval named patient use programmes, other patient support and disease management

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')*
		programmes, surveys of patients or healthcare providers, compassionate use or name patient use, or information gathering on efficacy or patient compliance in which adverse event reporting is actively sought.
483-485		Comment: For more detailed clarification and consistency throughout the document the sentence should be amended Proposed change (if any): suspected adverse reactions originating from compassionate use or named patient use conducted in Member States where the active ~~collection~~ sought of adverse events occurring in these programmes is 484 not required (see VI.C.1.2.2.).
561-562		Comment: For more detailed clarification and consistency throughout the document the sentence should be amended Proposed change (if any): expressed by the primary source, the case should not be downgraded to a report of non-not causally related adverse event with regard to reporting obligations.
744-746		Comment: For more detailed clarification and consistency throughout the document the sentence should be amended Proposed change (if any): Medicinal products used in critical conditions or for the treatment of life-threatening diseases, vaccines, contraceptives are examples of such cases. This applies unless the reporter has specifically stated that the outcome ~~was due to~~ of disease progression was due to a lack of therapeutic efficacy and is therefore ~~was~~ not related to the medicinal product.
1349- 1350		Comment: For more detailed clarification and consistency throughout the document the sentence should be amended

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')*
		Proposed change (if any): A patient support programme is an organised data collection system where a marketing authorisation holder actively soughts and collects information relating to the use of its medicinal products with regard to efficacy and/or safety.
2263		Figure VI.2. Business process map - Follow-up of ICSRs by marketing authorisation holders Comment: The process is confusing regarding "Request missing info from primary sources". Sometimes the primary source is unknown or not reported to the MAH (e.g. report received by MAH from competent authority). Proposed change (if any):
2267		VI.App.1.2 Follow-up of ICSRs by competent authorities in Member States involving consumers or healthcare professionals Comment: Regarding "Request missing info from primary source": As per today, this is conducted differently by the EU NCAs. Some NCAs do not perform follow-ups. It should be harmonized how many attempts for follow-ups should be done at least. Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016

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

Comments from:

Name of organisation or individual
PrimeVigilance Ltd.

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 number *(To be completed by the Agency)*	General comment	

2. 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')*
1851		Comment: When a significant case correction is made following internal review (or expert review) of a previously reported ICSR, can the data element A.1.7 'Date of receipt of the most recent information for this report' be changed to the date when the correction was identified. (Until the switch to E2B (R3) is made.)
724-725		Comment: Reports of … abuse…with no associated adverse reaction should not be submitted as ICSRs. However, GVP Annex I (EMA/876333/2011 Rev 3) includes the following under the definition of a 'Serious adverse reaction': Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as … development of dependency or abuse. The IME list includes PTs Drug abuser and Substance abuser. Proposed change: Consider drug abuse as serious ADR and submit such reports to EudraVigilance.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>
October 14th, 2016

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

Comments from:

Name of organisation or individual
QuintilesIMS

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 number *(To be completed by the Agency)*	General comment	
	QuintilesIMS wish to share the following comments and recommendations, which derive from our cumulative experience as a provider of solutions that drive healthcare forward : • With regards to Non-Interventional studies, we believe that the requirement to collect and report Adverse Events / Reactions (AE/ADRs) as Individual Case Safety Reports (ICSRs) and as aggregated reports should be limited to primary data sources and should not include databases or other secondary data sources, unless the study objectives require the collection of AE/ADRs from databases or other secondary data sources. • We recommend adding clarity on the adverse events collection and reporting requirements for studies that leverage both secondary and primary data collections. • We believe that GVP Module VI would benefit from adding further emphasis on the need for risk-proportionate pharmacovigilance activities.	

2. 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')*
724-728		Comment: We suggest adding further emphasis on the need to plan for **risk proportionate** pharmacovigilance activities, specifically in relation to reports of overdose, abuse, off label use, misuse, medication error or occupational exposure. Proposed changes: VI.B.6.3.Replace "*They should be considered in periodic safety update reports as applicable*" by a more specific statement, referring to the risk proportionate approach to be adopted as part of the risk management plan. Add references to GVP Modules V and VII.
959-964 998-1001		Comment: We recommend to clearly define the AEs collection and reporting requirements for non interventional post authorisation studies that leverage both secondary and primary data collections, for instance studies where medical records data considered as a secondary data source are enriched with data collected directly from Health Care Professionals and/or from patients. Proposed change: VI.C.1.2.1. Combined study designs based on primary and secondary data collections are currently addressed as a footnote (33). We suggest adding a new sub-section in the body of the text, stating "*In combined study designs, based on primary data collection and secondary use of data, collection of adverse events and submission of ICSRs is required exclusively from data collected directly from the Health Care Professionals or patients, unless the protocol justifies a different provision.*"
1002-1004		Comment: Relatively to studies that leverage secondary data or databases, the text states that reporting of suspected adverse reactions in the form of ICSRs is not required, however suggests that AE/ADRs from secondary data sources need to be collected, collated and presented in aggregated form. Databases typically include a high volume of cases, which are difficult to identify and extract, difficult to validate (difficult determination of the causality assessment or lack thereof), difficult to be followed-up upon, and at high risk of duplicate reporting. In addition, the associated high workload might detract resources from more efficient and

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')*
		risk-tailored PV activities. Our recommendation is for GVP "Reporting rules for non-interventional post-authorisation studies" to clarify that collection of AE/ADR from secondary databases is not required, unless it is directly linked to the study objectives. Proposed change: section VI.C.1.2, b) we recommend text amendment as follows: "*For these studies, the collection and reporting of suspected adverse reactions in the form of ICSRs is not required. Aggregated reporting of AE/ADR is not required, unless directly related to a specific study objective and justified in the protocol.*"

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

Name of organisation or individual
STALLERGENES

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).

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment

2. 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')*
Lines 408-409		Comment: If a suspected adverse reaction is notified both in the frame of a post-marketing study and spontaneously, it is unclear whether the case should then be managed only as spontaneous and excluded from the study analysis or not. Indeed, it appears difficult - for data retrieval purpose - to classify the suspected adverse reaction as spontaneous if it is part of a post-marketing study. Please provide more details on how these cases should be handled. Proposed change (if any): In this aspect, the following situations should also be considered as spontaneous reports: [...] • Cases notified by different reporters, referring to the same patient and same suspected adverse reaction, and at least one notification is done in an unsolicited manner for Eudravigilance reporting purpose; These cases should be therefore excluded of the study analyses.
Line 1851 (table)		Comment: ICH E2B(R2) format did not support amendment reports, and therefore it was leading to situations where the reports were considered as late. As ICH E2B(R3) introduces the use of 2 dedicated fields for amendments, how will compliance be calculated on these cases by the Agency? For example, after *internal review* by an expert of a case, the seriousness is upgraded and the case becomes serious. Will the submission of the amendment be considered as non compliant? Moreover, as regards to Product Quality investigation results or any other information provided by an internal

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')*
		department, when the results are available after the case has been submitted, how should this information be managed (Follow-up or amendment)? Please provide more details on how the amendments will be managed by the Agency in Eudravigilance. Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

October 14th 2016

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

Comments from:

Name of organisation or individual
Xendo - Vigilex [redacted] Website: www.xendo.com□

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 number *(To be completed by the Agency)*	General comment
	Comment: The current consultation document refers to IMP and NIMP while the new clinical trial regulation (536/2014) refers to auxiliary products. Proposed change (if any): To avoid any confusion, this document should be linked to the updated clinical trials Regulation

2. 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')*
654 - 659		Comment: What are the expectations of the Agency for confirming the proficiency of the PV staff working in SMEs? How to determine the proficiency level? Are there any standards available ? Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

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

Comments from:

Name of organisation or individual
ZEINCRO HELLAS S.A

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 number *(To be completed by the Agency)*	General comment
	We have no general comments.

2. 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')*
Line 295 and Reference (3) bottom of the page		Comment: please consider rephrasing the line 295 as to not include absolute reference of the revision of the Medical Device Vigilance guideline as this guideline could be updated in the future and this would mean that the GVP should also be updated to reflect changes. Furthermore, the link provided by clicking to the MEDDEV 2.12-1 rev 8 reference at the bottom of the page does not guide you to Med Dev. Proposed change (if any): please see comment above
Line 299-300		Comment: please consider keeping the term suspected adverse drug reaction (SADR) instead of individual case safety report (ICSR) because an ICSR is created from a reported SADR as also seen in lines 354-355. Proposed change (if any): In accordance with ICH-E2B, the primary source of the information is the person who reports the facts of a suspected adverse reaction.
321-322		Comment: please consider omitting this sentence as the reporting source still stands even if the medically qualified person has personal relations with the patient. The "medical identity" is sufficient to qualify as a medically confirmed case. Proposed change (if any): sentence to omit- "Similarly, a report may be submitted by a medically qualified patient, friend, relative or carer of the patient.

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')*
405-407		Comment: please provide examples of "information materials" could these be: DHPCs, PILs, RMP education materials? Proposed change (if any):
408-409		Comment: Please clarify this statement. If a report is received both by a solicited source (ex. PSP) and directly by the patient would this be consequently considered an unsolicited spontaneous report? Should this statement be rephrased to state that if the same report arrives via a solicited and an unsolicited manner this should be considered solicited and related so it is subsequently entered in EudraVigilance as such? Proposed change (if any): please see comment above
413		Comment: Please add a bullet point before the beginning of the sentence as to align with the rest of the section. Proposed change (if any): please see comment above
488		Comment: Please consider omitting the phrase "suspected adverse reaction" as a valid case contains by definition a suspected adverse reaction. Proposed change (if any): Valid cases should be sent according the modalities detailed in VI.B.7 and VI.B.8
501		Comment: please change the symbol (·) after the words phone number to a full stop. Proposed change (if any): please see comment above

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')*
512		Comment: please add a full stop after the word descriptors Proposed change (if any): please see comment above
509		Comment: please define the term age group. For example, if a report states that the patients participating in a study had a mean age of 40 and one of these patients experiences an ADR is this considered a valid criterion of an identifiable patient? Proposed change (if any):
701		Comment: Please add information on the reasons we need to collect breastfeeding cases even when there is no AE reported (as the title of the section is "**use** of a medicinal product **during** pregnancy or **breastfeeding**" and the breastfeeding paragraph then states: **suspected adverse reactions** which occur in infants **following exposure** to a medicinal product.") Proposed change (if any):
707-716		Comment: Since the following, VI.B.3., mentions follow-up requirements regarding age, please consider omitting this paragraph as it may be considered misleading because it can be interpreted that paediatric and elderly population of medication use are special situations which means that documenting of use is necessary regardless of the presence of adverse events Proposed change (if any): remove VI.B.6.2
1073		Comment: please inform if the phrase "arising from an error" means arising from a medication error.

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')*
		Proposed change (if any):
1212 and 1214		Comment: please add a semicolon (;) instead of a comma at the end of the points "d" and "e" as done in the above a,b and c sections. Proposed change (if any): please see comment above
1998		Comment: The first bullet point starting with "Data element B.4.K.19…..should be provided as applicable" is repeated also in lines (and tables) 2027 and 2038. Proposed change (if any):

Please add more rows if needed.