25 June 2012
EMA/428850/2012
Patient Health Protection

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

GVP Module VI – Management and reporting of adverse reactions to medicinal products

The first seven good-pharmacovigilance-practice (GVP) modules on prioritised topics were released for public consultation between 21 February and 18 April 2012. The modules have been revised, taking the comments received into account.

Those who participated in the public consultation were asked to submit comments using the specific templates for each module and the definition annex.

The comments received are published for each module, 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.

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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)

Comments from:

Name of organisation or individual
Asociación Española de Farmacéuticos de Industria (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*).*

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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')*
316-317		This paragraph states that the frequency of the monitoring of special sites or digital media should depend on the risk associated to the medicinal product. Proposed change (if any): It will be very useful for Pharmaceutical Industry to establish a specific period of time of each kind of risk.
321-325		Comment: In relation to cases from the internet or digital media, the identifiability of the reporter refers to the existence of a real person, that is, it is possible to verify the contact details of the reporter (e.g., a valid e-mail address has been provided). Could you please clarify if we should consider the case as a valid case if we don´t receive answer from the reporter after contacting with her/him by e-mail? Proposed change (if any):
577-579		This section (VI.B.1) states only the requirement for the "expedited reporting of valid serious ICSRs" while in section VI.C.3 “Expedited Reporting time frames” (lines 968-976) shows the expedited reporting time frames for serious valid ICSRs and non-serious valid ICSRs. Section VI.C.3 is cross-referenced to section VI.B.1, and taking this into account the information provided in VI.B.1 would be incomplete.
1775-1778		This paragraph stated that until standards for the electronic transmission of attachments (e.g. copies of literature articles) are developed in the framework of ICH, the sender should follow the rules outlined below for the submission of a copy of the literature article as detailed in VI.C.6.2.3.2. If copyrights were excluded in Pharmacovigilance area the safety of the population will increased as the submission of the case will be earlier. Proposed change (if any): Copyrights should not be considered for Pharmacovigilance purposed.

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.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We have significant concerns over the requirement for MAH to monitor non-company owned or controlled websites. MAH should not be obliged to monitor the internet and other digital media which it does not own or control. The current proposals would constitute a significant bureaucratic burden which is unlikely to be value added , do not appear consistent with the risk proportionality principles enshrined in the legislation and importantly, are unlikely to result in improved public health protection. We request a six months transitional period (until January 2013) for the implementation of this module to update existing processes with new 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')*
135-178		Comment and proposal: All definitions should be removed and cross reference to the definition annex should be made instead in order to avoid inconsistencies and unnecessary repetitions. For exemple, the definition of misuse is different to the one on of the GVP annex definition line 223.
280-282		Comment: A systematic literature review in one of widely used reference databases should be sufficient. This would be in line with lines 1607-1608 ("It is best practice to have selected one or more databases appropriate to a specific product."). Proposed change of line 281: review "at least in one" of widely used reference databases (e.g. Medline, Excerpta Medica or Embase) … In addition it is strongly recommended that the frequency of this literature review follows a risk based approach. For medicinal products with a well established use we deem it sufficient to review literature every three month. This is in line with the recommendations of e.g. the BfArM in its 6th Announcement relating to the Notification of Undesirable Effects and Abuse of Medicinal Products which contains feasible recommendations (No 3.2.1). Proposed change: the frequency of the literature review should be determined following a risk based approach.
284-286		Comment: "All company offices are encouraged to be aware of publications in their local journals …" The current requirement – as written - could provoke a quite high and disproportionate workload. Proposed change: In addition, all company offices are encouraged <u>to conduct an assessment</u> of their local scientific and medical journals to evaluate whether potential ADRs have been published in these local journals.
293-295		Comment: This requirement contravenes the principle spirit of the management of literature articles in that duplicate reporting by different MAHs should be avoided. An adverse reaction occurring in a particular country will be reported by the MAH who markets the product in that particular country. Therefore a separate MAH who has never launched the product (and may never launch it in the future) should not *report* the article

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		about an ADR which occurred following administration of another company's product to avoid case duplications. Proposed change: The sentence should be deleted: ~~This also applies to reports identified in the scientific and medical literature that originate in a country where a company holds a marketing authorisation but has never commercialised the medicinal product.~~
317-332		Comment: We have deep concerns over this requirement. MAH should not be obliged to monitor the internet and other digital media which it does not own or control. The current proposals would constitute a significant bureaucratic burden which is unlikely to be value added , do not appear consistent with the risk proportionality principles enshrined in the legislation and importantly, are unlikely to result in improved public health protection According to Directive 2010/84/EU, the packaging information leaflet includes a standardised text expressly asking patients to communicate any suspected adverse reaction to doctors, pharmacists, healthcare professionals or directly to the national spontaneous reporting system. Therefore it is inappropriate that the MAH should monitor in addition special internet sites or digital media. MAH may only monitor those sites which it owns or controls. We do not think non-company sponsored sites, including those recommended to be actively monitored should be monitored using conventional adverse event collection. CIOMS V states there is no obligation to report adverse events from secondary care databases as the information does not originate from defined projects and can be generated by multiple individuals for various reasons and uses. This rationale applies to non-company sponsored sites in today's digital era. Furthermore, in monitoring non-company sponsored sites, there are risks of duplicate reporting and concerns around feasibility and appropriateness of follow-up. We consider that such data may be used as an adjunct to conventional spontaneous adverse event collection and not entered into the company safety database. Proposed changes: Delete lines 317-321 and replace by <u>The MAH is not expected to routinely screen external (non-company sponsored) websites for information on adverse events.</u> Line 322: *Unsolicited cases of suspected adverse reactions from ~~the~~* ***company sponsored*** *internet or digital*

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		media should be handled as spontaneous reports. Line 325 – 328: This text creates a 'grey area' for non-company sponsored sites that the MAH accesses and may become aware of an AE. Most internet forums require membership before you privately contact via a direct messaging 'button'. Proposed change of line 325: *In relation to cases from ~~the~~* ***company sponsored*** *internet or digital media…* We propose to insert the following guidance: For cases from non-company sponsored internet or digital media (where the MAH has accessed the site and become aware of the event) the identifiability of the reporter should only be verified privately through direct communication. Where direct (private) communication can only be achieved through subscription to the website (e.g. creating a specific site account), the reporter should be considered as invalid. In this scenario, the MAH shall not be required to follow-up the report, either publicly or privately. Delete lines 330-332.
358 - 360		Comment: From this text, a written report of an AE from a physician who did not provide any address/contact details would be invalid, where as a telephone call from a consumer providing would be valid if confirmed verbally? Proposed change: ~~For the reporter to be considered identifiable, contact details need to be available in order to confirm or follow-up the case if necessary. All parties providing case information or approached for case information should be identifiable, not only the initial reporter~~. If a reporter does not wish to provide contact details (e.g. address), 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.~~ Name, initials and/or qualification have been recorded.
374-379		Comment: This paragraph would suggest that incomplete (invalid) cases that are missing at least one of the four elements should be recorded within the pharmacovigilance system for use in ongoing safety evaluation activities. This is open enough to imply that suspect product and/or suspected ADR can be missing.

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		Proposed change: Reports ~~for which~~ ~~the minimum information is incomplete~~ where an identifiable reporter and/or an identifiable patient are not verified should nevertheless be recorded within the pharmacovigilance system for use in ongoing safety evaluation activities.
400-401		The request for confirmation in writing will not be workable in practice because it will be overly burdensome for MAHs and HCPs, even if pre-populated forms are used to reduce burden. The implementation of such an administrative requirement is opposed to the general aim of the new pharmacovigilance legislation which is to rationalise and streamline the system. Proposed change: Replace the following text from line 400 as indicated: ~~*Written confirmation of details given verbally should be obtained whenever possible.*~~ For cases indicating potentially important risks, the marketing authorisation holder should consider to seek written confirmation of details given verbally.
450		The requirement to regularly review databases to identify duplicates ICSRs will be disproportionately burdensome. It should be sufficient to perform the duplicate check at data entry stage, potentially also to perform a duplicate check during generation of aggregated reports. Proposed change: Delete line 450: ~~*Databases should be reviewed regularly to identify and manage duplicates ICSR. a*~~nd replace with: *A procedure shall be in place to account for identification and management of duplicate cases on a regular basis.*
465 - 469		Comment: Training in pharmacovigilance legislation in addition to specific AE reporting training does not make sense for sales personnel. This will only cause confusion. Proposed change: Staff directly performing pharmacovigilance activities, and other personnel working in other departments who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be ~~appropriately trained in~~ aware of applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities for which they are

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		responsible and/or undertake
494-497		Comment: classification of serious reports in pregnancy cases: " reports of congenital anomalies or developmental delay ……" This assumes that there are new serious criteria added but not added to the definition of seriousness thus not aligned to line 218 of GVP module VI, nor the definition of 'serious adverse reaction' (cf. GVP definition annex line 376-391). Proposed change: ensure consistency with serious adverse reaction i.e. remove reference to developmental delay.
514-517		Comment: The wording implies that when a spontaneous report is received without specification of the age/age group, follow-up attempts have to be made to obtain such information. Stratification of safety information per age groups has the objective to identify new age-group specific adverse events, differences in the nature of known adverse events, long term effects or new information on under- or over-dosing. The proposed wording would mean that follow-up has to be sought even for well known non-serious adverse event reports if no age information is provided. This is an inappropriate use of resources which is also not in line with the recommendations of CIOMS Working Group V for follow-up approaches or the Guideline on Conduct of Pharmacovigilance for Medicines used by the Pediatric Population (Doc.Ref.EMEA/CHMP/PhVWP/235910/2005- rev.1.) Proposed change: The collection of safety information in the paediatric or elderly population is important. ~~Every attempt should therefore be made to obtain and submit the age or age group of the patient.~~ For such safety reports where neither information on age or the age group of a patient is provided careful medical consideration should be applied to decide whether follow-up has to be sought to obtain such information.
527-535		Comment: The decision whether or not further follow-up is required should be made after careful medical evaluation for each individual case. Such evaluation should follow a risk-balanced approach. In cases entailing relevant overdose relapse (for example coma) the MAHs will have a high interest in obtaining as much follow

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		up information as possible. At the opposite, it does not add value to collect follow up only for completeness sake in cases with acknowledged and typically transient (self-limiting) adverse relapse of an overdose. Accordingly the request to conduct follow-up on every single cases without applying a risk balanced approach is against the spirit of focusing pharmacovigilance on what is medically relevant. Proposed wording: Reports (of overdose, abuse, misuse, medication error or occupational exposure) associated with suspected adverse reactions should be subject to expedited reporting according to the same criteria as other ICSRs. ~~They should be routinely followed-up to ensure that the information is as complete as possible with regards to symptoms, treatments and outcomes.~~ Careful medical evaluation should take place to decide on the need for further follow-up to ensure that the information is as complete as possible with regards to symptoms, treatments and outcomes.
557 - 561		Comment: This definition allows for interpretation where reports are received by electronic systems and not accessed by the MAH on the same date. We suggest taking the wording of the MHRA Purple Guide definition. Proposed change: Only valid ICSRs (see VI.B.2) should be reported. The clock for expedited reporting of a valid ICSR starts as soon as the information containing the minimum reporting criteria ~~has been brought to the attention of~~ becomes available to the national or regional pharmacovigilance centre of a competent authority or of any personnel of the marketing authorisation holder, including medical representatives and contractors. This date should be considered as day zero.
944-946		Comment: The requirement serves to capture delayed onset adverse reactions. In the scenario where no marketing authorisation remains in the EEA but products with the same active substance continue to be marketed outside of Europe the reporting requirements with regards to non-EEA cases should be ceased. Otherwise expedited reporting of new onset third country cases will continue forever subsequent to commercial withdrawal from the EEA market. Proposal: At the end of section VI.C.2.2.8. an additional sentence should be inserted as follows: If no marketing authorisation from the holder remains within the whole of the EEA, expedited reporting of third country case information can be terminated, while cases from EEA countries referring to the suspended EEA marketing authorisations will continue to be reported.

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1244-1251		Comment: It is common practice in industry that no or abbreviated case narratives in line with CIOMS V are written for non-serious expected safety reports to make efficient use of available resources and to focus on important safety information. The section about case narratives as proposed does not provide clarification whether the approach detailed in CIOMS V is still acceptable and it is desirable to have clarification on this. Proposed change: An example of a standard narrative template is available in the Report of the CIOMS Working Group V[35]. In line with CIOMS Working Group V[35], for non-serious expected safety reports the requirement to provide a stand alone full narrative does not apply.
1296-1299		Comment: this is an example of unclear use of the " wording " expedited manner". Expedited can be both 15 or 90 day rule Proposed change: considered as significant changes and thus reported under 15 days.
1456-1463		Comment: In line with the recommendations of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider' we suggest to code the reported quality defect as close as possible to the reported verbatim to allow an accurate analysis of such reports. For example, a patch adhesion issue should be coded to "medicinal patch adhesion issue (LLT term code 10069938)" and not to the less specific term "product quality issue". The latter should only be used if no accurate LLT term is available. An appropriate search strategy still allows retrieving all product quality issues as appropriate. Proposed change: Where an adverse reaction(s) report is associated with a quality defect of a medicinal product, the MedDRA Lowest Level Term closest to the reported verbatim should be selected to code for the quality defect. If no matching Lowest Level Term is available the code 10069327, corresponding to the term "Product quality issue", should be added to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1.b).
1731-1738		Comment: The exclusion criteria for articles from the literature provided in lines 1731 to 1738 should be

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		consistent with the exclusion criteria as provided in line 835 to 838 which reads as follows: *"Where ownership of the medicinal product by the marketing authorisation holder can be excluded on the basis of the active substance name, formulation, route of administration, primary source country or country of origin of the suspected adverse reaction, the ICSR should not be reported to the competent authorities in Member States, or to the EudraVigilance database"* Proposal: The text in line 1731 exclusively mentions another company's branded medicinal product as reason for exclusion. Behind this first sentence, the following should be added to reflect the identical conditions as outlined in lines 835-838: Articles can be excluded from reporting by the marketing authorisation holder if another company's branded medicinal product is the suspected medicinal product. Alternative reasons for exclusion of a published article are when either of the following not consistent with the marketing authorisation holder's medicinal product presentation: the active substance name, formulation, route of administration, primary source country or country of origin of the suspected adverse reaction, the primary source country, the country of origin of the suspected adverse reaction.
1824		Table VI.3 The order of the sections 3 and 3.1 should be changed. It seems to be more appropriate first to check whether the case is serious and then whether the case is from EU. See also line 1839, Table VI.6 "final arrangements".
Minor/editorial comments		
189		Comment: Use of "Since" is confusing at the start of the sentence Proposed change: or trade names of the medicinal product. A medicinal product is authorised with a defined
293		Comment: "This also applies.." use of these words is confusing Proposed change (if any): Reword
845		Comment: surplus "s" after "article" Proposed change (if any): literature article describes adverse reactions, which occur in a group of patients with a designated

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 APRIL 2012

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

Comments from:

Name of organisation or individual
ALEXION Europe SAS

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Alexion recognises the high level quality and completeness of this module as compared to what was in Volume9A. It will be of great support for PV systems management and continuous improvement.

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 146 to 156		Comment: by considering causality in the frame of spontaneously reported ICSR there is a risk that numerous spontaneous not are not expedited or even not taken into account in Pharmacovigilance systems. Some Pharmacovigilance systems use indeed detailed causality scales for spontaneous ICSRs assessment, such as that from WHO UMC, broken down into "certain", "Probable/likely", "Possible", "Unlikely" and so on. The ICH E2D definition for an adverse reaction refers to that from ICH E2A guidance and thus includes per se the notion of causality. This ICH E2A definition states: " …adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event". In some systems this is interpreted as "should be at least possibly related" and thus used as a threshold for expedited reporting. There is thus a risk that a number of spontaneous ICSRs assessed as "unlikely" related by the MAH and/or the reporter will not be taken into account in the Pharmacovigilance dataset. Although the current module tries to anticipate this in stating: "For regulatory reporting purposes, as detailed in the ICH-E2D guideline, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse reaction. Therefore all spontaneous reports submitted by healthcare professionals, patients or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the reporters specifically state they believe the events to be unrelated" the GVP should be reinforced in this respect. Proposed change (if any): Suggestion would be to rephrase as follows: "For regulatory reporting purposes, as detailed in the ICH-E2D guideline, if an event is spontaneously reported, regardless of level of relationship assessment, it meets the definition of an adverse reaction. Therefore all spontaneous reports submitted by healthcare professionals, patients or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the reporters specifically state they believe the events to be unrelated"
Line 254		What is meant by reports must be "validated"? Does this means against source data or by a health care professional? This concept needs to be clarified in order to avoid any confusion.
Line 313		Comment: Alexion would like to question and comment on the recommendation " that the marketing authorisation holder actively monitor special internet sites or digital media such as those of patients' support or special diseases groups in order to check if they describe significant safety issues which may necessitate reporting in accordance with the recommendations described in VI.C.2.2.6. The frequency of the monitoring of those sites or digital media should depend on the risks associated to the medicinal product"

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		First question: if this recommendation stays as is will the fact for a MAH not to monitor such media be considered as a non-compliance and lead to established finding during inspections with subsequent potential sanctions? It is practically not feasible to establish a systematic review process of those media the number of which can be high and the perimeter of which is difficult to determine. Furthermore it may be more that difficult to identify at least both a reporter and a patient within the posted information. Finally reliability of contained information could be questioned as www is not a controlled environment and MAH could be facing fake data without having the possibility to confirm it. In addition, this is in contradiction with lines 249- 250 statement saying that data must be verifiable in VI.B.1: "The system should be designed so that it helps to ensure that the collected reports are authentic, legible, accurate, consistent, verifiable and as complete as possible for their clinical assessment." Proposed change (if any): Suggestion would be to manage safety information only from such media owned by the MAH or for which the MAH gives grants.
Line 1731 VI.App2.7. Day zero		Comment: There should be in this appendix a section about the management of articles in foreign languages such as non EU languages and allowance for taking into account as Day zero, either when it is initial ICSR or follow up information, the date by which the translation in English, or any other language the company is able to understand, becomes available to the MAH or concerned third party if any. Proposed change (if any): A paragraph could be added to section VI.App2.7. Day zero as follows: "Initial or follow up information in a publication containing the minimum information for a reportable adverse reaction or potential relevant follow up information may not be available in a language comprehensible for the MAH. In that case, Day zero will start at the date the translation is available either to the MAH or the third party if any. Translation should be obtained in a reasonable timeframe".

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17th April 2012

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

Comments from:

Name of organisation or individual
AstraZeneca

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	AstraZeneca welcomes the opportunity to provide feedback to GVP Module VI – Management and reporting of adverse reactions to medicinal products (EMA/873138/2011). AstraZeneca has had the opportunity to contribute to the EfPIA comments and agree to those. Additionally, AstraZeneca would like to provide one further specific comment.

2. Specific comments on text

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1246-1247		**Comment:** The narrative should not be required to contain 'relevant laboratory evidence (including normal ranges)'. Where this is available it should be provided as structured data and thus not necessary to reproduce in the narrative. This approach should not prevent peak values (etc) being described. **Proposed change (if any):** Please delete "relevant laboratory evidence (including normal ranges)". The text should then read: ..... containing all known relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical course of the event(s), diagnosis, adverse reactions and their outcomes, ...

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
Austrian Federal Office for Safety in Health Care / Austrian Agency for Health and Food Safety

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	1):

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')*
384-390		Comment: According to these lines patient´s judgement has more value than the HCP´s opinion in relatedness of drug-event. A possible consequence of this situation could be the generation of signals by not medically educated persons. Proposed change (if any): For the purpose of more distinct signal evaluation the possibility to distinguish between medically confirmed and not medically confirmed consumer reports should be given in EVDAS as well as the information about any different causality assessment (e.g. definite exclusion of causal relationship) by a HCP.

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)

Comments from:

Name of organisation or individual
Bayer HealthCare

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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	A definition of a transitional period would be desirable, in order to define until when all requirements have to be implemented, as the final requirements will be available in July 2012 (e.g. Member state requirements for non-serious EU ICSRs; lines 1011-1012). Is there a timeline, until when the list of scientific and medical literature and active substances monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004 will be provided?
865-871	Comment: It is important that all stakeholders involved in signal detection have systems in place to clearly identify ICSRs as relating to such falsified medicinal products. Reporting and signal management processes should ensure that such ICSRs are clearly separable and are not affecting signal evaluations for genuine products. Proposed change: Add "*Reporting and signal management processes of all involved stakeholders should ensure that such ICSRs are clearly separable and are not affecting signal evaluations for genuine products*" after lines 865-871.

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)*	
378 and 1889 378		Comment: We acknowledge the need to provide applicable data of invalid cases for auditing purpose and appropriate processes should be in place to ensure that such data are retrievable. However, invalid cases "should not be used for scientific evaluation" (see line 1889). The otherwise conflicting statement in line 378 should be modified as stated below. Proposed change: Reports for which the minimum information is incomplete should nevertheless be recorded ~~within the pharmacovigilance system for use in ongoing safety evaluation activities~~.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 April 2012

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

Comments from:

Name of organisation or individual
British Generic Manufacturers Association (BGMA)

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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Duplicate check. There seems a lack of information in what is expected regarding duplicate checks. i.e. how Before a case is reported to Eudravigilance – how will potential duplicates be identified? What if a report is sent to both the MAH and NCA/Other Agency? Presumably the MAH should be checking before submitting? Also the CA should be checking
	Definitions It should be absolutely clear earlier in the module that all **valid** reports non-serious **and** serious are considered 'expedited', it is only that the timelines are different. People currently associate expedited only with serious cases, and they could make assumptions in their interpretation that this is still the case. I was a bit confused initially, and commented on a later section, but have now removed that comment as I later confirmed the definitions. It would be useful in case people do not bother to read on. Suggest a definition of an expedited case earlier – e.g. under Section VI.A.2.6? And refer to VI.C.3 p 28 e.g. Expedited case = Any valid ICSR, serious or non-serious report. Serious to be reported in 15 days, non-serious to be reported in 90 days And also a definition of valid report, under Section VI.A.2.7? cross-referring to VI.B.2 p 11 e.g. A valid ICSR must contain the 4 minimal criteria.
	This module seems to be all about collection and recording of ICSRs by CAs and MAHs and putting them in Eudravigilance or their own systems. There is nothing I can see about how reports received direct by the CAs will be actively shared with the MAHs. I presume the MAHs would have a responsibility to review Eudravigilance periodically and find any company product reports they do not already have? How then would an MAH get that report into their system? I have not seen anything mentioning the responsibilities to monitor Eudravigilance either for duplicate checks, for cases or for safety signals (the safety signalling module doesn't obviously cover this). It seems that the priority is for the Agency to have all the cases, but not for the MAHs to be notified

Stakeholder number *(To be completed by the Agency)*	General comment
	on cases on their products. Is this covered in another module somehow? I fear I am missing the point somewhere. I would be happy to be wrong. If it is covered in another module then cross-refer to it.
	If a case is nullified from Eudravigilance, how will MAH be notified? There could be a number of cases which remain in the MAH safety database.
	Some SMEs consider the document to be too long and repetitious, without significant added value. The tables in the Appendices are difficult to follow.

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')*
142		Comment: An event could be unintended but not necessarily noxious, e.g. a patient has suffered from tinnitus for many years and various standard treatments have made no difference; the patient than takes Product X for a completely unrelated indication, and the tinnitus stops. Proposed change (if any): ".....noxious and/or unintended...."
149 - 151		Comment: "reasonable possibility" is too limited (black or white, yes or no). Some companies may prefer more stratification, but this could be covered internally in their database. Proposed change (if any): e.g. Likely, probable, possible, unlikely, etc.
168		Comment: Typo - subjects Proposed change (if any): Should be "subject"
193		Comment: I had to look up what 'mutatis mutandis' means. It is a legal term which means "by changing those things which need to be changed" (Wikipedia). This definition didn't really help me understand. Not sure how many other people will understand it Proposed change (if any): The guidance in this Module also applies "in principle, with appropriate changes where necessary, " to medicinal products.....etc?
206-207		Comment: The definition of a consumer does not mention carer - this would be a useful category Proposed change (if any): "....patient, lawyer, carer, friend, ..."
294-295		Not clear. Does this mean the MAH can assume no causal association if the product has not been marketed in that country?
317-321		Comment: This 'recommendation' to monitor special internet sites and patient support or disease area seems potentially onerous for generic companies who have many products often of wide-ranging therapeutic groups.

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 including " if appropriate" i.e. It is also recommended that the marketing authorisation holder actively monitor special internet sites or digital media such as those of patients' support or special diseases groups, if appropriate' in order to check.....
328/329		Comment: "If the country of the primary source is missing, the country where the information was received should be used as the primary source country, depending where the review takes place." It is possible that more than one NCA or MAH may pick up the same ICSR in different countries via digital media. According to this process, if the country is not known, the country identifying the report should be used as the primary source country. There is a risk that the NCAs and MAHs will submit the same report to their systems under different countries, so elimination of duplicate reports will be problematic. In addition, different MAHs could pick the same ICSR up in other countries and do the same thing. Proposed change (if any): This risk should be highlighted, and that the MAHs and the NCAs should put in place systems to minimise the risk of duplicate reports. Or, maybe they could invent a dummy country to whom these would be reported? It is actually difficult to see how duplication can be avoided. Within an MAH at least – the corporate centre could be alerted and ensure only one case is entered.
327/328		Comment: Typo. "....described in a non-company sponsored digital media, the report....." Proposed change (if any): Should read, EITHER, "....described in a non-company sponsored digital medium, the report.....", OR "....described in non-company sponsored digital media, the report....."
353		If a literature case and qualification of reporter is unknown, can the reporter be identified by the lead authors initials?

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')*
384/385		Comment: It should be reinforced strongly in the text that the ICSR cannot be nullified/deactivated/deleted from the PhV system. I appreciate that it is actually fairly obvious, but I think it is worth reinforcing here. Proposed change (if any): Add. If a healthcare professional on follow-up does not consider the adverse event to be related, the report should not be nullified or deactivated from the Pharmacovigilance system.
403-406		Comment: This suggests use of a potentially several targeted specific forms. Too many targeted specific forms could be very difficult to manage and maintain and assess for complete information. Proposed change (if any): Add as appropriate. i.e. The use of targeted specific forms, if considered appropriate, should avoid the requirement to duplicate.....
435		Comment: Who are the stakeholders (this term has not been used before) that are referred to? MAH, EMA, CAs, co-licence, co-marketing partners, etc? Proposed change (if any): Define what is meant by stakeholders.
435		Comment: "Case report information should only be transmitted between stakeholders in an **anonymous** format". If the stakeholders referred to includes third party companies who are marketing the products of the MAH,. If the reports are received anonymised then the MAH will not be able to follow-up the reports. Proposed change (if any): Suggest include:"If a third party company is marketing the product of an MAH, the third party company should request and endeavour to obtain documented permission from the reporter for the MAH to contact the reporter direct, or they should advise the reporter who the MAH is and provide them with contact details to enable them to report to the MAH direct.
452		Comment: Refers to regulatory organisations. How does this differ from NCAs and the Agency? I note that the phrase is

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')*
		used again later (line 478 – but not again at all). Proposed change (if any): If it differs from NCAs and the Agency, this should be made clear. Suggest add definition of NCAs and Agency to Annex 1 Definitions? If it doesn't differ then why use it?
487		Comment: Individual exposure during pregnancy cases with an "abnormal outcome are classified as serious" and should be expedited. Given the definition now of expedited, then this is a bit confusing for me where it is positioned with old reporting requirements in my head. Proposed change (if any) At the start of the pregnancy section (line 473) insert something like. "Any valid ICSRs that occur in the mother or the embryo or foetus that have been exposed to a medicinal product during pregnancy should be expedited and reported according to seriousness."
533		Comment: Occupational exposure: In some cases occupational exposure could apply to exposure to the key ingredient. This could be impossible to report against a particular medicinal product or manufacturing batch even. It would be useful to explain how reports should be submitted in this case. Will the product dictionary allow for such a report?
596-602		Comment: Not clearly stated when new versions of the standard formats are released when they should be implemented. If this information is available elsewhere the reader should be clearly directed to where the information is available. (We had MedDRA update issues in the UK where the MHRA did their update earlier than they should have done) Proposed change (if any): Suggest "For guidance on when updates should be implemented – see Section ????. or reference????"
649		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')*
		Typo. "The reporting rules of solicited reports to the EudraVigilance database modules are dependent **of** the types of organised collection systems." Proposed change (if any): The reporting rules of solicited reports to the EudraVigilance database modules are dependent **on** the types of organised collection systems.
660 + 664		Comment: The reporting of CT events depends on the 'nature of the intervention'. This should direct the reader to what this means. Proposed changes (if any): Add "Refer to ??????", or perhaps it could simply be i.e. they are interventional...or is it a bit more complicated than that?
709-711		Comment: "Unless there are justifiable grounds resulting from pharmacovigilance activities, individual Member States shall not impose any additional obligations on marketing authorisation holders for the reporting of suspected adverse reactions." What would be **justifiable** grounds for an individual MS to impose additional obligations. This leaves the door wide open for NCAs to have different requirements. Who will agree/decide what is justifiable? The Agency? The Committee? This seems to blast a hole through the harmonisation concept. Having said that, there may be valid reasons – such as where there is a lot of sun - monitoring re. photosensitivity reactions. Proposed change (if any): Maybe this is there somewhere, but something about who to contact in the event of a desire to challenge the CAs or the Agency? Who would arbitrate?
732-741		Comment: " or any company not belonging to the same company or group of companies but having concluded commercial agreement with the company...

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')*
		What exactly does "commercial agreement" include? Supply agreements, regulatory agreements, any other agreements that are product related? Does concluded mean finalised or cancelled? It is assumed that "concluded" means "entered into" usually and we could suggest this wording. It is also assumed that this paragraph is directed to those marketing a product and not the range of contractual partners. Please confirm This paragraph is not clear.
750 + 763		Comment: Solicited reports from data collection systems. Please confirm – reading VI.C.2.2.2. and VI.C.6.2.3.7 suggests that all solicited (serious or non-serious) should be databased). Fine. It does not say whether or not solicited non-serious should be expedited. It does mention inclusion of these in the PSUR. Proposed change (if any): I think should be confirmed/clarified that the non-serious solicited do not need to be expedited (assuming this is the case). In addition, there needs to be confirmation that only related should be collected or, should it be all? And what about event reported on other non-Company drugs – should it be recommended to report ot the other MAH?
777-781		Comment: "Other reports of adverse reactions, suspected to be related only to medicinal products which are not subject to the scope of the study, and where there is no interaction with the studied medicinal product(s), should be reported to the concerned competent authorities where applicable by the investigators Is it expected that the MAHs will advise the investigators that this is their responsibility? It is expected that the MAHs should also database these reports or at least receive them in a study report? Also when it says reported, does it mean expedited?

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')*
822-828		Comment: Is there a timeline to agree the list of active ingredients and journals that will be monitored by the Agency?
831		Marketing authorisation holders should also make themselves aware of publications in local journals. Will the local CA provide guidance regarding additional local journals, as presumably compliance would be assessed?
839		Comment: Expedited reporting of literature ICSRs from a CA database outside EU – I currently database these for inclusion in the PSUR. Surely, CAs ultimately report to WHO and further expedited reporting would be duplication?
860		Comment: VI.C.2.2.4 Suspected adverse reactions related to quality defect or falsified medicinal products. It is important to include if possible the origin of the suspected falsified medicine in the ICSR report eg. Since it's essential regarding public health or possible recalls if the falsified product was bought (eg. Internet) or brought illegally from outside EU or was it bought from local pharmacy.
931-933		Comment: Literature searches for generic products from submission until approval are unnecessary and excessive. Proposed change (if any): Ensuring that the established medicine SmPC is in line with the reference product SmPC, at the time of submission, and if appropriate following referrals during assessment, is more appropriate.
939-942		Comment: Literature searches for generic products from submission until approval are unnecessary and excessive. Proposed change (if any): Ensuring that the established medicine SmPC is in line with the reference product SmPC, at the time of submission, and if appropriate following referrals during assessment, is more appropriate.
949		Comment: How long after withdrawal or revoking an MA should monitoring continue? Proposed change (if any): Suggest include monitoring until the last batch of product has expired.
943		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')*
		There is no mention of responsibilities in the event that there is a change of ownership e.g. a product may be available in the marketplace from MAH 1, but the MA was transferred to MAH 2. Procedures should be in place to assure appropriate exchange of cases and follow-up (PSURs will be an issue here also)
956		Comment: VI.C.2.2.10 Reports from class action lawsuits "Where large batches of potential ICSRs are received, marketing authorisation holders may request, in exceptional circumstances, for an exemption in order to submit serious cases of suspected adverse reactions within 30 days from their date of receipt instead of 15 days." Very positive improvement. Proposed change (if any): The process of how exemption is requested and approved should be clearly defined.
1010		Comment: Interim process. Non-serious should be reported 'if required' to the CA in the country of occurrence. What do they mean by 'if required'. This opens the door to non-serious expediting in different countries at different times i.e. inconsistency. Proposed change (if any): Examples of what they mean? Might help. Different CAs making different demands a concern
1146 - 1149		Comment: Will "request the sender to re-transmit the ICSR" be considered during inspections as a compliance issue? Wouldn't electronic transmission essentially mean that there should not be any missing information as such? It is always possible when an initial report is received that information will not be complete. Proposed change (if any): Please could this point be clarified. It should be made clear that this is NOT a failure in transmission.
1146- 149		There is no mention if there is a failed transmission, that the initial date submission was attempted will 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. I mention this as sometimes transmission fails for reasons on both sides, and it should not be the case that compliance is compromised as a result. Proposed change (if any): Include a statement that all dates of attempted submission are recorded in the systems
1295-1311		Comment: Do the statements "always necessitates medical judgment" and "medical judgment should be applied" mean this should be done by a medic/medically qualified person? Not always necessary and appears excessive, in many circumstances assuming the assessors are suitably qualified. Proposed change (if any): The judgment of an experienced/qualified person as to whether input from a medic is needed should be sufficient.
1369		Comment: Why "maintain" a duplicate case in the ICSR database? What does maintain mean/involve? Could lead to further duplicates if not managed correctly. Proposed change (if any): Consider replacing "maintain" with "retain".
1585-1592		Can this be appealed?
1593-1596		Literature search is performed irrespective of commercial status – surely the period from submission to authorisation is outside this range? Proposed change: Delete last sentence.
1605		Comment: All example databases given are fee/subscription based. This means MAHs, particularly of SMEs have another significant cost and registration to maintain, assess and review. With no alternatives for SMEs to consider. Proposed change (if any): Include reference to PubMed (free, uses similar journals to MedLine, web based, no registration required). Or add, "or other recognised appropriate systems may be used."
1627 - 1638		Comment: Upon reading this section it is not clear what message is being conveyed. It appears to read as a point of fact rather than guidance.

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: Suggest add 'Select relevant search limits'?
1655		Comment: There is mention of searching literature for excipients with pharmacological effects. As there is guidance already available for excipients with known pharmacological effects will it be necessary to involve such excipients in routine literature searches. This seems excessive for generic products where excipients are well known and widely used. We appreciate that this is not mandatory, but some guidance as to which excipients these might be would be useful. Proposed change (if any): Add a reference to a suitable source?
1712		Comment: "Full citation....should always be retrieved and reviewed" – perhaps clarify if this is what's available on screen (heading is 'Outputs') or ordering of the full article? - could be extremely costly for companies. Also, for a safety article why would the complete paper be needed if an informative abstract is available containing sufficient information to constitute a valid report and allow reasonable assessment i.e. in the case of a generic product. Proposed change (if any): Full citation is only needed if minimum four data elements and a reasonable assessment of the case is not possible from the abstract, or no abstract is available is not available. Full citation is only needed if a PSUR is to be submitted for the product or a potential safety issue is identified.
1716 - 1717		Comment: "qualified to identify the article of relevance" - how are they qualified? Proposed change (if any): Experienced and/or qualified.
1721-1725		Most companies perform separate literature searches – a weekly to identify ICSRs only and a product-specific for PSUR purposes. The benefit of this will be more pronounced now that PSUR requirement will drop. Proposed change: Delete paragraph 1721-1725.
1749 - 1753		Comment: "check to prevent reporting of duplicates" - this is easy on the internal MAH database. How will this work for checking of duplicates reported via other routes? For example a doctor reports to the MAH, the pharmacist reports directly to the EMA and the consumer reports to local CA; none of them checks with/or informs the other that they are reporting this case.
1574		Comment: Flow chart design not clear and is over-complicated. It starts badly with the first question being "Was the reporter able to provide the missing information?" It does not match the words in the table.

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): Simplify/clarify
1784		Should consideration of potential copyright be instead shared? The MAH has already paid for the article. Proposed change: Perhaps per #1782, 'sent according to the local requirements' should encompass whether article can legally be attached or not as agreed between MAH and CA.
1821		Comment: Title not clear Proposed change (if any): Expedited reporting of suspected adverse reaction in the EU – interim arrangements.
1819, Appendix 3 1820 and 1837		Comment: What about a duplicate (and validity) check prior to a new case being opened?
1820		Comment: (the flow-chart) This is I think the first place that it is clear that MAHs are not required to expedite non-serious **non**-EEA case to Eudravigilance. Proposed change (if any): Mention under VI.B.7?
1881		Comment: What happens if a case is nullified by the Competent Authority ("sending organisation") – how will the MAH find out about this?
1899		Comment: The flow chart does not start the flow clearly, but I think I can figure it out with the words.
1910		Comment: "check to prevent reporting of duplicates" - this is easy on the internal MAH database. How will this

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')*
		work for checking of duplicates reported via other routes? For example a doctor reports to the MAH, the pharmacist reports directly to the EMA and the consumer reports to local CA; none of them checks with/or informs the other that they are reporting this case.
1914, Number 2		Comment: who are the Duplicate Management Team? Not mentioned previously. What is their remit? How will they be managed? What processes will they follow? What is the referral process for disputes about duplicates?

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

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

Comments from:

Name of organisation or individual
Bundesverband der Pharmazeutischen Industrie e. V. (BPI) - German Pharmaceutical Industry Association

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
	The line-numbering is not the same comparing published document of this Module under the EMA homepage with published document of this Module sent before. It could be a deviation of 1 or 2 lines.

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 195 - 196		**Comment**: It is stated that the primary source of the information on a suspected adverse reaction(s) is the person who provides information about the case. According to ICH-E2B the person is not reporting the case but the facts (ICH-E2B: line 362 – 363). **Proposed change (if any):** The sentence should be changed to: "The primary source of the information on a suspected adverse reaction(s) is the person who provides information about the facts".
Line 211 - 213		**Comment**: Do reports coming from friends and relatives of medically qualified people should really be managed as coming from a HCP if there is no evidence that the medically qualified person provided any input in the report?
Line 280 - 282		**Comment**: Definition of criteria for journal selection would be beneficial (e.g. impact factor, advisory board, other)
Line 289-299		**Comment**: If a company never commercialised the medicinal product in a country, why should a publication be considered by the concerned MAH? **Proposed change (if any):** Delete the sentence.

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 307 - 308		**Comments**: It is stated that marketing authorisation holders should regularly screen internet or digital media under their management or responsibility, for potential reports of suspected adverse reactions. **Proposed change (if any):** It is suggested to change the sentence as follows: "Marketing authorisation holders should regularly screen internet or company sponsored digital media under their management or responsibility, for potential reports of suspected adverse reactions".
Line 313 - 325		**Comment**: Recommendation to screen internet sites of patients, to handle unsolicited reports as spontaneous reports and to verify the contact details – this is not feasible. In those internet sites the patients should be privacy protected. A MAH should not contact a patient in those internet sites. All patients will be informed via the new PILs to report adverse side effects e.g. electronically to authorities. Registering of unsolicited cases is not reasonable. Registering of email-addresses without active reporting of the patient to the MAH and without permission of the patient contravenes against data protection. Is there a national legislation providing for such actions? **Proposed change (if any):** Delete the passage.

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 326 - 328		**Comment**: If it does not qualify for expedited reporting, which action is proposed? **Proposed change (if any):** Describe the action proposed.
Line 351 - 352		**Comment**: It is stated: "For the reporter to be considered identifiable, contact details need to be available in order to confirm or follow-up the case if necessary." We are wondering if the contacts details are considered to be the sine qua non condition for the identification of a identifiable reporter (in that case initials or qualifications would not be enough). In our eyes clarification / re-formulation is needed.
Line 405 - 407		**Comment / Proposed change (if any):** correction of the following sentence is needed: "Similarly, prospective reports of pregnancy should be monitored to obtain information on the outcome at the expected date of delivery."
Line 514 - 520		**Comment**: How should that be realized (specially for unauthorised populations)? Why differentiation made with regards to unauthorised populations, while AR definition makes no reference to in label use anymore.
Line 542 - 551		**Comment**: Lack of efficacy is not applicable in cancer chemotherapy. E.g. if an antineoplastic drug has a rate of complete

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')*
		or partial remission of 20% this means, that 80% will have a progression or stable disease. It is not reasonable to register the 80% of cases as case of lack of efficacy. **Proposed change (if any):** Insert: "in cancer therapy, stable disease or progression of disease should normally not be classified as lack of efficacy."
Line 680 - 683		**Comment / Proposed change (if any):** correction of the following sentence is needed: "Standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients or consumers shall be developed by the Agency in collaboration with Member States in order to collect across the EU harmonised information relevant for the evaluation of suspected adverse reactions, including suspected adverse reactions arising from an error associated with the use of medicinal products [REG Art 684 25].
Line 761 - 783		**Comment**: In oncologic and rheumatologic NIS, it would be an extensive workload and not useful to send non-serious cases from these NIS expeditedly in 90 days. E.g. hundreds and thousands of cases with nausea, fatigue, etc. Which exceptions could be made? Will it from already initiated NIS also be obligatory to send those cases expeditedly or does it only apply for new NIS beginning after July 2012? **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')*
		delete requirement to send non-serious cases from NIS in 90 days.
Line 766 – 768 Line 776 - 778		**Comment**: It is mentioned that such reports shall be included in the CSR. We feel it should also be mentioned to include it in the PSUR.
Line 859 - 860		**Comment / Proposed change (if any):** correction of the following sentence is needed: In addition, in order to protect public health, it may become necessary to implement urgent measures such as the recall of one or more defective batch(es) of a medicinal product from the market.
Line 914		**Comment / Proposed change (if any):** correction of the following sentence is needed: "lack of supply of medicines."
Line 951		**Comment**: According to the definition mentioned in section VI.B.1.1. (unsolicited reports) and VI.B.1.2. (solicited reports) a report may be only solicited or unsolicited. Thus "stimulated unsolicited reports" are not defined. Proposed change (if any): The term "stimulated unsolicited reports" needs to be changed to "solicited reports": "Reports arising from class action lawsuits should be managed as solicited reports"

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')*
		or a new definition for "stimulated unsolicited reports" is needed.
Line 1022 - 1023		**Comment**: It is stated that competent authorities in Member States shall submit all serious ICSRs that occur in their territory to the EudraVigilance database. But in Directive 2010/84/EU Article 107a it is mentioned that each Member State shall record all suspected adverse reactions that occur in its territory which are brought to its attention from healthcare professionals and patients ... and should submit the reports electronically to the Eudravigilance database. **Proposed change (if any):** It is recommended to be in line with the wording provided in the directive 2010/84/EU: Competent authorities in Member States shall submit all serious ICSRs that occur in their territory and which are brought to their attention from healthcare professionals and patients to the EudraVigilance database.
Line 1072 - 1073		**Comment / Proposed change (if any):** correction of the following sentence is needed: The ICH-M5 guideline 'Routes of Administration Controlled Vocabulary' (CHMP/ICH/175860/2005), which provides standard terms for routes of administration.
Line 1095 - 1097		**Comment**: What is about other unsolicited reports, beside spontaneous? Would unsolicited not be more appropriate -

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')*
		instead of spontaneous? Furthermore, correction is needed: "The adverse reaction reports collected in the EudraVigilance Post-Authorisation Module (EVPM) refer to spontaneous reports and solicited reports which do not fall under the scope of the Clinical Trials Directive 2001/20/EC (see VI.C.2.2.2)."
Line 1553 ff		
Line 1723 - 1723		**Comment**: It is mentioned that articles can be excluded from reporting by the marketing authorisation holder if another company's branded medicinal product is the suspected medicinal product. In the absence of a specified medicinal product source and/or invented name, ownership of the medicinal product should be assumed for articles about an active substance. Alternative reasons for exclusion of a published article are a specified formulation or a route of administration that is not consistent with the marketing authorisation holder's medicinal product presentation. On the other hand in section VI.C.2.2.3. (line 829 – 832) it is stated: "Where ownership of the medicinal product by the marketing authorisation holder can be excluded on the basis of the active substance name, formulation, route of administration, primary **source country or country of origin** of the suspected adverse reaction, the ICSR should not be reported to the competent authorities in Member States, or to the EudraVigilance database. 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')*
		The "source country or country of origin" should also be mentioned in section VI.App2.6., line 1723 – 1723.
Line 1814		**Comment:** Table VI.3 The order of the sections 3 and 3.1 should be changed. It seems to be more appropriate first to check whether the case is serious and than whether the case is from EU. See also line 1839, Table VI.6 "final arrangements".

<Date of submission>

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

Comments from:

Name of organisation or individual
Celgene Europe 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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	No comment provided

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 1578 **Table VI.1.** Process description - Identification of biological medicinal products. Step 2		Reference: Are batch number, brand name & active substance all present and identifiable? — If Yes, create the case and send it to the correct receiver (step 3). If there is more than one batch number, structure the batch number that coincided with the adverse reaction in the Drug section (ICH-E2B (R2) B.4) and enter the other batch numbers in the case narrative. If No, create the case and send it to the correct receiver (step 3) and follow-up with the reporter (step 2.1). — MAH/NCA Comment: B.4.k.3 allows for multiple batch lot number each separated by the delimiter defined by the transmission chosen. There is a character limitation of 35 Alpha-Numeric. Multiple batch numbers can be all structured and the batch number that coincides with the adverse reaction should be the first of the concatenation. Proposed change (if any): Step 2 description should be reworded as follows: If Yes, create the case and send it to the correct receiver (step 3). If there is more than one batch number, structure first the batch number that coincided with the adverse reaction in the Drug section (ICH-E2B (R2) B.4) followed by the other batch numbers. If No, create

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 case and send it to the correct receiver (step 3) and follow-up with the reporter (step 2.1).

<Date of submission>

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

Comments from:

Name of organisation or individual
Chugai Pharma UK Ltd

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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')*
VI.C.2.2.3. :Reports published in the scientific and medical literature:		Literature articles which only detail patients in tables or line listings should not be reported as ICSRs. Even if there are the minimal information to be validated for expedited reporting in section VI.B.2. we don't have to submit the ICSR as expedited reporting to the competent authorities.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17.04.2012

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

Comments from:

Name of organisation or individual
CIS bio international/IBA

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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')*
Lines317-321		Comment: Some web-sites that are not under MAH's responsibility request to be a member of the patient association, affected by a specific disease. How can we monitor such organisations? On which criteria a web site should be "monitored "or not? Furthermore, a company could be considered as a spy when monitoring the chats of the association members! Establishing a consistent, updated list of relevant web sites could be problematic since new ones are frequently created . Proposed change (if any):
Lines 993-1018		Comment: when the Interim arrangements are forecasted to be ended? Proposed change (if any):
Lines 502-505		Comment: Some drugs have a relative contraindication in pregnancy (i.e. are used when benefit>risk). Example Tc- albumin macroaggregates used for the diagnosis of pulmonary embolism. Do you consider an expedited reporting is mandatory? Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

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

Comments from:

Name of organisation or individual
DK - Danish Health and Medicines Authority

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Comment: It is important that the various kinds of adverse reactions are identified in the reports in order to ensure that EMA, national competent authorities and the marketing authorization holders are able to act appropriately. Specific information in relation to the new elaborated definition of an adverse reaction needs to be provided in a clear structured way when reports of adverse reactions are submitted. Information on e.g. medication errors, misuse, abuse or off-label use should be specifically reflected in submission forms to ensure that the information is provided on reported cases and can be utilized in evaluation of data. Comment: Requirements/expectations regarding the clinical/medical assessment of cases are missing in the document. This is an essential point which often leads to discussion during inspections.

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')*
250		Comment: It should be stated that the clinical assessment should be documented and so should the qualifications of the person performing the clinical assessment. Proposed change (if any): Addition of a sentence stating that the clinical assessment should be documented and so should the qualifications of the person performing the clinical assessment.
293		Comment: This should be in line with lines 556-557 Proposed change (if any): It should be 'the regulatory reporting clock starts as soon as the marketing authorisation holder, <u>including medical representatives and contractors</u> has knowledge that the case meets the minimum criteria for expedited reporting.
Section VI. B.3.		Comment: Follow-up of reports. It should be stated that 'Attempts to collect missing information should be documented'. Proposed change (if any): Insertion of the text: 'Attempts to collect missing information should be documented'.
Section VI.B.4.		Comment: It should be stated that data entry should be subject to quality control. In line 450 'data entry' should be added. Proposed change (if any): Insertion of text: Data entry should be subject to quality control.

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')*
		In line 450 'data entry' should be added.
Line 455:		Comment: If certified copies of source data are accepted, the procedure to generate certified copies should be described and validated. Proposed change (if any): addition of text regarding certified copies.
Line 462:		Comment: staff receiving telephone calls e.g. receptionists and 24/7 contractors should also be listed. Proposed change (if any): Addition of text regarding receptionists and 24/7 contractors.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
Drug Commission of the German Medical Association; D-10623 Berlin, Herbert-Lewin-Platz 1, Germany

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The Drug Commission of the German Medical Association (DCGMA) thanks for having given the opportunity to comment on the Guideline on good pharmacovigilance practice. The DCGMA is taking the opportunity to make some general comments to 'Module VIII – Post authorisation safety studies' followed by detailed proposed changes of the text and will also propose changes to the Module V and Module VI.

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 311-321		Comment: The question arises here – and should be addressed – whether or not a company is obliged to run its own website as a "receptor" for direct ICSR reports (from healthcare professionals or consumers).
Line 362		Comment: The list of information characterising a patient seems unclear and hence inappropriate: The word "or" implies that any single one of the characteristics could suffice. This means that e.g. "a female patient" would be considered sufficient. This is too little information to allow reasonably accurate identification of the patient and to avoid or detect duplicates.
Lines 400-411		Comment: We strongly agree that follow-up methods should be conducted in ways that encourage health care professionals to submit additional information and that motivate them to report adverse drug reactions again in the future. However, in our experience extensive questionnaires without any pre-populated data fields are common practice by some MAH to obtain follow-up information. In some cases, these questionnaires are sent to the primary source only in English language. Proposed change (Lines 406-407) In follow-up report forms information already provided in the initial report should be pre-populated in the corresponding data fields to make their completion by the primary source less burdensome. Follow-up report forms have to be provided in the national language of the primary source.
Lines 525 and 1236-1259		Comment: In both sections, ADR reports originating from situations of medication error, other kinds of inappropriate medication, or of medically well justified off-label use should be given special attention. In addition to judgement about relatedness between medication and adverse event (creating a reportable ICSR) it is always

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')*
		crucial whether just the fact that the medicine was used other than officially recommended/authorised created the adverse event, and if so, what might have been the cause of the deviation from what is recommended/authorised (root-cause-analysis). It should be kept in mind that some kind of deviation from "standard" underlies about every second ICSR and is worth analysing.
Lines 533-535		Comment: Expedited reporting does not seem appropriate in all cases included here. Reports of medication errors should contain additional information on the context the error occurred to enable a valid case assessment. Proposed change (Lines 533-535): The case report should contain a detailed description of the incident including information on prescription, administration, transcription or dispensing. Additional information about the type of medication error (wrong prescription, dosage error, sound- or look-alike, wrong transcription…) as well as the context should be reported according to the MedDRA terms.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4th April 2012

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

Comments from:

Name of organisation or individual
Drug Safety Research Unit

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Our comments relate to the implications of the guidance on organisations that conduct intensive monitoring studies, such as the Drug Safety Research Unit (DSRU). We believe that findings from intensive monitoring studies should continue to be reported via interim and final study reports, not by submission of Individual Case Safety Reports (ICSRs). Submission of ICSRs from our event monitoring studies has neither scientific nor public health benefits. When the DSRU studies produce safety information, it would usually define the total safety profile of the product or come under the "Emerging Safety Issues" category, rather than the ICSR category. This opinion has been made known at ENCePP meetings and other gatherings to senior EU regulatory Pharmacovigilance colleagues who were all in agreement with it.

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')*
Below line 784 Line 771		Comment: We believe that findings from intensive monitoring studies should be reported via interim and final study reports, not by submission of Individual Case Safety Reports (ICSRs). Proposed change (if any): To clarify the requirements for reporting from intensive monitoring studies, we suggest either insertion of additional bullet point below line 784, as follows: *Adverse reaction reporting is not required from intensive monitoring studies (such as DSRU Modified Event Monitoring and Specialist Cohort Monitoring studies and Lareb Intensive Monitoring). All adverse reactions/ events received in such studies should be summarised in the aggregate interim study reports and final study reports.* Or, addition of the following statement at the end of the first paragraph of section VI.C.2.2.2.1 (line 771): *(such as DSRU Modified Event Monitoring and Specialist Cohort Monitoring studies and Lareb Intensive Monitoring).*
Line 770		Comment: Medical records are commonly referred to as *medical notes*, rather than *medical charts*. Proposed change (if any): we recommend that "chart" is changed to "notes", as this is the term usually used in English.
Line 1116		Comment: Proposed change (if any): we suggest removal of "intensive monitoring".

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
EFPIA – European Federation of Pharmaceutical Industries & Associations

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	EFPIA welcomes the detailed and generally helpful guidance provided in this module and in particular the fact that it aims to address the fact that technology has advanced exponentialy since a number of ICH guidelines, as well as Volume 9A Eudralex were originally written. In this respect, we broadly agree with the requirements for company sponsored sites, recognising that these may evolve over time. EFPIA however has significant concerns regarding the new proposal to routinely monitor digital media sources which are not company sponsored. The current proposals would constitute a significant bureaucratic burden which is unlikely to be value added , do not appear consistent with the risk proportionality principles enshrined in the legislation and importantly, are unlikely to result in improved public health protection. We do not think non-company sponsored sites, including those recommended to be actively monitored should be monitored using conventional adverse event collection. CIOMS V states there is no obligation to report adverse events from secondary care databases as the information does not originate from defined projects and can be generated by multiple individuals for various reasons and uses. This rationale applies to non-company sponsored sites in todays digital era. Furthermore, in monitoring non-company sponsored sites, there are risks of duplicate reporting and concerns around feasibility and appropriateness of follow-up. EFPIA considers that such data should be used as an adjunct to conventional spontaneous adverse event collection and not entered into the company safety database. Third parties have leapt ahead of industry and regulators in the use of non-company sponsored digital data for analysis of medicine safety, pragmatically and at a fraction of the cost. Persisting with regulator and industry use of an inappropriate regulatory framework for this source of data is not in the interests of public health or patient safety. We provide proposed rewording in the detailed comments section below (lines: 310-332).
	Comment: There seems to be an inconsistent interpretation of the term 'expedited' throughout this document now that non-serious reports have to be reported within 90 days.

Stakeholder number *(To be completed by the Agency)*	General comment
	Proposal: We propose that the term ‘expedited’ should refer to 15 day reports only.

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')*
158 & 364		**Comment**: There is an inconsistency in the reporting requirement for unrelated spontaneous reports in line 158 versus line 364. Line 158 speaks only of "unrelated", i.e. as per ICH definition, whereas line 364 speaks about excluding a causal relationship. **Proposed change**: Line 158: change to state that unless the reporters specifically state that a causal relationship can be excluded as per section VI.B.2., i.e., "*Therefore all spontaneous reports submitted by healthcare professionals, patients or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the reporters specifically state ~~they believe the events to be unrelated~~* ***that a causal relastionship can be excluded****."*
160-178		**Comment and proposed change**: The definitions in this section should be the same as those outlined in GVP Annex I – Definitions
284 and 831-832		**Comment**: The requirement for local literature review is inconsistent between line 284 (all company offices are encouraged to be aware of publications) and 831-832 (journals in those Member states where the medicinal product is authorised). **Proposed change**: Revise lines 831-832 to read: *"Marketing authorisation holder****~~s~~ country offices*** *should also make themselves aware of publications in local journals in those Member States where the medicinal product is authorised and report valid ICSRs as appropriate."*

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')*
307		**Comment**: The phrase "Every attempt…" is too strong in this scenario. **Proposed change**: Revise to read: ~~*Every attempt*~~ "***Reasonable attempts****…"*
310-332		**Comment**: VI.B.1.1.4.Information on suspected adverse reactions from the internet or digital media: We broadly agree with the requirements for company sponsored sites, recognising that these may evolve over time. We do not think non-company sponsored sites, including those recommended to be actively monitored in lines 317-320 should be monitored using conventional adverse event collection, see General Comments for further details. **Proposed changes**: Delete lines 317-321: ~~*"It is also recommended that the marketing authorisation holder actively monitor special internet sites or digital media such as those of patients' support or special diseases groups in order to check if they describe significant safety issues which may necessitate reporting in accordance with the recommendations described in VI.C.2.2.6. The frequency of the monitoring of those sites or digital media should depend on the risks associated to the medicinal product."*~~ Replace lines 317-321 with: *"The MAH is not expected to routinely screen external (non-company sponsored) websites for information on adverse events. If external websites are screened (for whatever purpose), company involvement should 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')*
		transparent (if possible) and an appropriate process must be in place for the handling of any safety data generated. Appropriate methodology should be used for each activity, with the rationale documented appropriately, this document should be made available to the Competent Authority on request. The methodology can range from collection and analysis of every adverse event to a brief summary in a PSUR as appropriate." Line 322: *"Unsolicited cases of suspected adverse reactions from ~~the~~* ***company sponsored*** *internet or digital media should be handled as spontaneous reports."* Line 325: *"In relation to cases from ~~the~~* ***company sponsored*** *internet or digital media…"* Delete lines 330-332: *~~If a marketing authorisation holder becomes aware of a report of suspected adverse reaction described in a non-company sponsored digital media, the report should be assessed to determine whether it qualifies for expedited reporting.~~*
400-401		**Comment**: The request for confirmation in writing will not be workable in practice because it will be overly burdensome for MAH and HCPs, even if pre-populated forms are used to reduce burden. **Proposed change**: Delete the following text from line 400-401: *~~"Written confirmation of details given verbally should be obtained whenever possible."~~*

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')*
450		**Comment**: The requirement to regularly review databases to identify duplicates ICSRs will be disproportionately burdensome. It should be sufficient to perform the duplicate check at data entry stage, potentially also to perform a duplicate check during generation of aggregated reports. **Proposed change**: Delete line 450: ~~*"Databases should be reviewed regularly to identify and manage duplicates ICSR."*~~ And replace with: *"**A procedure shall be in place to account for identification and management of duplicate cases on a regular basis**."*
465 - 469		**Comment**: Line 465 to 469 states *"Staff directly performing pharmacovigilance activities, and other personnel working in other departments who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be appropriately trained in applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake".* We feel that training on "adverse event collection and reporting" is sufficient for other personnel working in other departments rather than training on applicable pharmacovigilance legislation and guidelines. Pharmacovigilance legislation and guidelines are extremely broad in scope and mostly not applicable to their role with the exception of AE collection and reporting. We propose training is therefore limited to this activity. **Proposed change**: Revise to read:

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')*
		"Staff directly performing pharmacovigilance activities, ~~and other personnel working in other departments who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control)~~ should be appropriately trained in applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake. ***Personnel working in other departments who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be appropriately trained in adverse event collection and reporting in accordance with internal policies and procedures."***
484		**Comment**: The phrase "Every effort…" is too strong in this scenario. **Proposed change**: Revise line 484 to read: *~~"Every effort~~* ***Reasonable attempts*** *should be made …"*
498-501		**Comment**: Reports of pregnancy exposure without outcome, with normal outcome or termination of pregnancy without malformation should not be subject to 90-day reporting, but need to be reported for PSUR purposes only. **Proposed change**: Revise to read (lines 498-501): *"Other cases, such as reports of termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data or reports which have a normal outcome, should not be reported on an expedited manner since there is no suspected adverse reaction. These reports should however* ***~~be processed as for other ICSRs~~ be collected and discussed in the relevant periodic safety update reports****."*
514		**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 phrase "Every attempt…" is too strong in this scenario. **Proposed change**: Revise to read: *~~"Every attempt~~* ***Reasonable attempts*** *should therefore be made …"*
533 - 535		**Comment**: Line 533-535 states: "*Reports (of overdose, abuse, misuse, medication error or occupational exposure) associated with suspected adverse reactions should be subject to expedited reporting. They should be routinely followed-up to ensure that the information is as complete as possible with regards to symptoms, treatments and outcomes."* The decision whether or not further follow-up is required should be made after careful medical evaluation for each individual case. Such evaluation should follow a risk-balanced approach. In cases entailing relevant overdose sequelae (for example coma) the MAHs will have a high interest in obtaining as much follow up information as possible. Reversely, it does not add value to collect follow up only for completeness sake in cases with acknowledged and typically transient (self-limiting) adverse sequelae of an overdose. Accordingly the request to conduct follow up on every case in the above categories as a routine without applying a risk balanced approach is against the spirit of focussing pharmacovigilance on what is relevant. **Proposed change**: Revise lines 533-535 to read: *"Reports (of overdose, abuse, misuse, medication error or occupational exposure) associated with suspected adverse reactions should be subject to expedited reporting* ***according to the same criteria as other ICSRs.*** *~~They should be routinely followed-up to ensure that the information is as complete as possible with regards to symptoms, treatments and outcomes.~~* *Medical evaluation should take place to decide on the need for further follow-up to ensure that the 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')*
		is as complete as possible with regards to symptoms, treatments and outcomes."
698-700		**Comment:** If the MAH was the primary reporter for an ICSR then appropriate follow-up with the reporter for additional information is the reposnsibility of the MAH. If member states do not involve the MAH, the reporter runs the risk of receiving follow-up requests from both the MAH and the Member state Competent Authority which would be confusing for the reporter and duplicative. **Proposed change**: Line 698-700, insert bold text: Amend wording to: *For reports submitted by a MAH, Member States on whose territory the adverse reaction occurred ~~may~~* ***should*** *involve the MAH in the follow-up of the reports*
708		**Comment:** In order to ensure timely availability of adverse event information in EudraVigilance, it is important that the phrase 'in a timely manner' (line 708) is replaced with an explicit timeline consistent with the timelines for marketing authorisation holders. **Proposed change**: Change to line 708: *… ~~in a timely manner~~* ***within 15 or 90 days for serious and non-serious reports respectively.***
750		**Comment:** 750 – VI.2.2.2. Solicited reports This section states that solicited reports arise from organised data collection schemes and lists what these activities could be. Some of these activities can generate reports that should be treated as spontaneous reports (see line 801 – Patient support programmes). **Proposed change:** Suggest the following edit to avoid readers misunderstanding this point: Line 753: *In the context of this module, these solicited reports are ~~those~~* ***often*** *derived from organised data collection schemes initiated, managed, or financed by marketing authorisation holders and that do not fall under the scope of the clinical trials Directive 2001/20/EC.…*
792		**Comment:**

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		792 - Section VI.C.2.2.2.2 references VI.A.2.2 for a definition, but that section does not contain a definition for compassionate or named patient use. **Proposed change:** Annex I – Include a definition for compassionate or named patient use.
801-818		**Comment:** Lines 267-268 (VI.B.1.1.1. Spontaneous reports) states: *A spontaneous report …does not derive from a study or any organised data collection schemes as defined in VI.B.1.2.* A similar statement is made in lines 334-336 regarding solicited reports. The above statements are contradicted in line 813-816 which state the following: *For organised data collection schemes where adverse event reporting is not solicited, any noxious or unintended response to a medicinal product which is notified to the marketing authorisation holder by a patient or healthcare professional should be considered as a spontaneous report of suspected adverse reaction and reported accordingly.* There is an apparent contradiction between the two sections which may lead to non-compliance. **Proposed change**: If lines 267-268 can not be changed (because they are in ICH E2D), we propose that lines 807-810 are amended as shown below to minimise confusion. ***It is recognised that according to the definition of a spontaneous report in ICH E2D that these***

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		cannot originate from an organised data collection scheme. However ~~*For*~~ *organised data collection schemes where adverse event reporting is not solicited, any noxious or unintended response to a medicinal product which is notified to the marketing authorisation holder by a patient or healthcare professional should be considered as a spontaneous report of suspected adverse reaction and reported accordingly,* ***despite the spontaneous event report definition in section VI.B.1.1.1.***
750-818		**Comment:** Lines 750-818 under section VI.C.2.2.2. Solicited reports: We propose to add a similar section on market research programmes as there is now for compassionate use and Patient support programmes. Market research is not per se a patient support programme, but can be an organised data collection scheme. Therefore, it would be welcome to get some more detailed guidance on handling these types of reports. **Proposed change**: Add a section VI.C.2.2.2.4 **'Market Research** ***Market research programmes are defined as the systematic design, collection, analysis and reporting of data and findings, relevant to Marketing and Business Development decision making.'*** ***Similarly to Patient Support Programmes, adverse event reports may be solicited or considered as a spontaneous report of suspected adverse reaction and reported accordingly.*** ***For market research services, or surveys where data are collected independently of an individual company and available to purchase to a number of Pharmaceutical companies who have not influenced the original design (including programmes referred to as Syndicated Patient Level Diary studies) there is no obligation on the supplier to report adverse events contained within the diaries to MAHs.***
850		**Comment:** Line 850 - currently states "The safety findings presented in these types of articles should however be

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		discussed in the relevant sections of the concerned periodic safety update report"... which is inconsistent with the PSUR section on Literature. The latter states that " This PSUR section should include a summary of new and significant safety findings, either published inthe peer reviewed scientific literature or mada available as unpublished manuscripts, when relevant to the medicinal product,that the MAH became aware during the reporting period"...so the elements of " new and significant" and " awareness " are missing in this module. **Proposed change:** The **new and significant** safety findings presented in these types of articles **which have become available to the MAH** should however be discussed in the relevant sections of the concerned periodic safety update report
904-906		**Commment:** The sentence *"Events may occur, which do not fall within the definition of reportable valid ICSRs, and thus are not subject to the expedited reporting requirements, even though they may lead to changes in the known risk-benefit balance for a medicinal product"* is not fully consistent with the provided examples. **Proposed change**: The above sentence should read: *"Events may occur, which do not fall within the definition of reportable valid ICSRs, and thus are not subject to the expedited reporting requirements, even though they may lead to changes in the known risk-benefit balance for a medicinal product* ***or impact on public health****".*
912-913		**Comment:** The definition of 'Emerging Safety Issue' used here should be aligned with that used in GVP Module IX (Lines 372-374) as well as with the definition of 'important risk' in GVP Module V. **Proposed change**: The text "*which impact on the risk-benefit balance of the medicinal product*" should read "*which impact on the risk-benefit balance of the medicinal product* ***and/or have implications for public health***"
921-928		**Comment:**

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		Line 916: VI.C.2.2.6 Emerging safety issues: The word 'forthwith' in the Directive is ill defined. The module makes clear that these notifications should occur only if the events/ observations affect the benefit: risk balance of a product, but then requires that this notification be done '*immediately when becoming aware of them*'. Line 1154: re-iterates the above requirement as it states '*immediately notified*' **Proposed change**: Replace and add to line 1154 '*immediately* ~~*when becoming aware of them,*~~ ***and no later than within 15 calendar days, if this affects the benefit risk balance of the product***'
950 – 955		**Comment:** Line 951-955 currently states "*A public health emergency is a public health threat duly recognised either by the World Health Organization (WHO) or the Community in the framework of Decision No. 2119/98/EC of the European Parliament and of the Council. In the event of a public health emergency, regular reporting requirements may be amended. Such arrangements will be considered on a case-by-case basis and will be appropriately notified on the Agency website.*" This language is very similar to language set out in section 5.12 of Vol 9A. However, the industry experience during the 2010 pandemic was that this language was entirely without use or effect. Agencies appeared powerless (or believed they were powerless) to amend the reporting requirements notwithstanding the provisions in 5.12 of Vol 9A. Therefore there is little point in repeating the language here without at least some amendment. Contrast the proposed approach in the EU with the approach in the US [Proposals for alternate reporting should include prioritization to enable focus on products/reports that are likely to have greater use or present a special concern or outcome. Reports with regulatory timeframes of 30 days or less should be submitted before periodic safety reports and delayed reports should generally be submitted within 6 months of restoration of the adverse event reporting process] (but in the absence of an agreed international

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')*
		approach the US guidelines alone are unlikely to be helpful in the event of an emergency). In the light of this experience this section might be improved by saying: **Proposed Change**: Replace and add to line 951-955: A public health emergency is a public health threat duly recognised either by the World Health Organization (WHO) or the Community in the framework of Decision No. 2119/98/EC of the European Parliament and of the Council. In the event of a public health emergency, regular reporting requirements may be amended . Such arrangements may be requested by MA holders and will be considered on a case-by-case basis ~~and will be appropriately notified on the Agency website~~ **by the Agency/European Commission within 7 days of receipt of the request. The outcome will be communicated to the applicant in writing without delay. Guidelines on the application of these procedures will be published by the EU Commission in line with comparable international guidelines by the end of 2012.**
961		**Comment:** Line 961 – VI.C.2.2.10. Reports from class action lawsuits: EFPIA welcome the inclusion in the guidance of an exemption to ICSR reporting in extenuating circumstances. **Proposed change**: We agree with the proposed exemptions for serious reports. In addition, we request an exemption for follow-up reports of up to 60 days for a company that has received a large batch of legal cases, consistent with the situation in the US.
1017-1018		**Comment:** We appreciate the inclusion of an Appendix to summarize the member state requirements for reporting of serious non-EU ICSRs and non-serious EU ICSRs in the final Module. We propose to include a requirement to maintain this Appendix updated through the EMA website.

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		Proposed change: Insert after line 1018: *To ensure compliance, Appendix 3.1 will be maintained as a living document on the EMA website throughout the duration of the transitional period*
1244 - 1245		**Comment:** It is common practice in industry that no or abbreviated case narratives in line with CIOMS V are written for non-serious expected safety reports to make efficient use of available resources and to focus on important safety information. The section about case narratives as proposed does not provide clarification whether the approach detailed in CIOMS V is still acceptable and it is desirable to have clarification on this. **Proposed change:** (line 1251), insert bold text: *An example of a standard narrative template is available in the Report of the CIOMS Working Group V.* ***In line with this, for non-serious expected safety reports the requirement to provide a stand alone full narrative does not apply.***
1731 - 1738		**Comment:** The exclusion criteria for articles from the literature provided in lines 1731 to 1738 should be consistent with the exclusion criteria as provided in line 835 to 838 which reads as follows: "Where ownership of the medicinal product by the marketing authorisation holder can be excluded on the basis of the active substance name, formulation, route of administration, primary source country or country of origin of the suspected adverse reaction, the ICSR should not be reported to the competent authorities in Member States, or to the EudraVigilance database" **Proposed change:** (line 1731) replace and insert bold text: *Articles can be excluded from reporting by the marketing authorisation holder if another company's branded*

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		medicinal product is the suspected medicinal product. ~~In the abscense of a specified medicinal product source and/or invented name, ownership of the medicinal product should be assumed for articles about an active substance.~~ Alternative reasons for exclusion of a published article ***can be when either of the following is not consistent with the marketing authorisation holder's medicinal product presentation: the active substance name,*** *formulation, route of administration,* ***primary source country or country of origin of the suspected adverse reaction****.*
1779-1783		**Comment:** Consideration of copyright may that mean the sharing of PDF versions of literature articles is not allowed. The MAH should only provide the literature reference on these occasions. **Proposed change:** (line 1779), insert bold text: *Literature articles reportable to the Agency should be provided in PDF format* ***(taking into account copyright considerations)*** *and sent via e-mail* Insertion in line 1783-1786: *marketing authorisation holders are recommended to consider potential copyright issues specifically as regards the electronic transmission and handling of electronic copies in the frame of regulatory activities.* ***When submission of a PDF is not allowed for reason of copyright, a literature reference will be acceptable.***
1821 Appendix 3-1 Process map figure (VI.3) 1824 Table VI.3 (Process description)		**Comment**: There is an inconsistency between lines 1007-1009: Competent Authorities in Member States should also make available to MAH of suspected products all serious ICSRs reported directly to them AND Lines 1821-1824: Appendix 3-1 Process map figure (VI.3) and Table VI.3 (Process description) which do not describe that NCAs should provide MAHs with the ICSRs they directly received; Step 12 in the table (page 59) mentions: sent to EV.

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		Proposed change: The process maps and description should be revised to also reflect the transmission of an NCA case to the MAH.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
EGA – European Generic Medicines Association

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	EGA stresses that it is urgent to know which national competent authorities will require the submission of non-serious ICSRs during the transitional period.
	Non-serious ICSRs from PASS should not be reported to competent authorities spontaneously. This information should be provided in the study report and PSUR, but not spontaneously, as it will increase the amount of work.

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 291- 295		Comment: This paragraph suggests that literature cases from countries where the product is not marketed need to be logged. Is this the case and if so, it contradicts lines 187- 192.
Lines 310-332		310 – VI.B.1.1.4.Information on suspected adverse reactions from the internet or digital media: Comment: The EGA broadly agrees with the requirements for company sponsored sites, recognising that these may evolve over time. The EGA does not think that non-company sponsored sites, including those recommended to be actively monitored in lines 317-320 should be monitored using conventional adverse event collection, see General Comments for further details. Proposed changes: Delete lines 317-320: ~~*It is also recommended that the marketing authorisation holder actively monitor special internet sites or digital media such as those of patients' support or special diseases groups in order to check if they describe significant safety issues which may necessitate reporting in accordance with the recommendations described in VI.C.2.2.6. The frequency of the monitoring of those sites or digital media should depend on the risks associated to the medicinal product.*~~ Replace lines 317-320 with: *The MAH is not expected to routinely screen external (non-company sponsored) websites for information on*

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 events. If external websites are screened (for whatever purpose), company involvement should be transparent (if possible) and an appropriate process must be in place for the handling of any safety data generated. Appropriate methodology should be used for each activity, with the rationale documented appropriately, this document should be made available to the Competent Authority on request. The methodology can range from collection and analysis of every adverse event to a brief summary in a PSUR as appropriate. Line 322: *Unsolicited cases of suspected adverse reactions from ~~the~~* ***company sponsored*** *internet or digital media should be handled as spontaneous reports.* Line 325: *In relation to cases from ~~the~~* ***company sponsored*** *internet or digital media…* Delete lines 330-332: *~~If a marketing authorisation holder becomes aware of a report of suspected adverse reaction described in a non-company sponsored digital media, the report should be assessed to determine whether it qualifies for expedited reporting.~~*
Lines 376- 378		Comment: How should articles in which patients are referred to as just 'five patients' etc, with no valid identifiers be treated? Should the equivalent number of invalid cases be created, or can we just include a summary of the article in the relevant PSUR?
Line 396		"… should be followed-up as necessary…". The EGA consideres that it should be stated that the efforts of follow-up depend on the significance of a case. A non-serious and/or serious listed case does not require an

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		active follow-up when the 4 minimal criteria are fulfilled.
Lines 400-401		Comment: As is written in line 405-406 the burden for the reported should be minimised as much as possible to assure the reporter also reports the next time. This means that asking the reporter for a written confirmation of the information as reported for example by phone is an example of needles burden to the reporter. Company experience shows reporters do think this is a waste of their time and efforts. Only for adverse events for which follow up information is required a form should be send and written follow up should be requested. Proposal: change the wording: … ~~Written confirmation of details given verbally should be obtained whenever possible.~~ *For ICSRs which are identified as requiring follow up this written follow up request* ~~routine pharmacovigilance activity~~ should be conducted…..
Lines 403-406		Comment: This suggests use of a potentially several targeted specific forms. Too many targeted specific forms could be very difficult to manage and maintain and assess for complete information. Proposed change (if any): Add as appropriate. i.e. The use of targeted specific forms, if considered appropriate, should avoid the requirement to duplicate…….
Line 450		The databases should be screened each time a case is received for duplicates. "Regularly" does not make sense because then the damage is done already.

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 719-725		Comment: This paragraph might lead to the understanding that only on the basis of sharing the route of administration but, for instance, not the active substance name, the MAH responsibility will apply. The EGA considers that MAH should focus their strength on collecting suspected adverse reactions related to medicinal products for which ownership cannot be excluded on the basis mainly of the active principle. The additional elements of information (formulation, batch number, route of administration, primary source country or country of origin) can help but should not constitute by their own elements of potential inclusion of suspected adverse reactions to be analysed. Proposed change (if any): Regarding the collection of suspected adverse reactions, marketing authorisation holders responsibilities apply to reports related to medicinal products (see VI.A.2.2) for which ownership cannot be excluded on the basis of the active substance name and formulation, batch number, route of administration, primary source country or country of origin of the suspected adverse reactions.
Lines 725 - 728		VI.C.2.2 Marketing Authorisation Holder responsibilities: Marketing authorisation holders shall ensure that any information on adverse reactions suspected to be related to at least one of the active substances of medicinal products authorised in the EU is brought to their attention by any company outside the EU belonging to the same mother company (or group of companies), which holds the marketing authorisation in the EU for the concerned medicinal product, or any company not belonging to the same company or group of companies but having concluded commercial agreement with the company who holds the marketing authorisation in the EU for the concerned medicinal product. Comment: From a PV perspective when outlicensing a product/dossier it becomes a stand-alone dossier where the partner is able to manufacture the product wherever he wants..

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 partner becomes responsible for PV, i.e. no need to exchange PV information. There is no relationship at all between the products. Only when the manufacturing site is the same, from a Quality perspective exchange of information should occur between the partner (MAH) and the manufacturer (the outlicensor) on e.g. quality defects in the product There is therefore no legal basis or ground to exchange information. Proposed change (if any): "…. or , *where relevant*, any company not belonging to the same company or group of companies but having concluded commercial agreement with the company who holds the marketing authorisation in the EU for the concerned medicinal product
Lines 785- 786		Comment: Why should there be doubt about reporting requirements? Should this not be clearly laid out in the relevant member states' legislation?
Lines 843- 849		Comment: Do these types of cases still need to be logged as non-valid cases, even if they are not reportable and don't contain identifiable patients (see comment on lines 376- 378).
Lines 862- 864		Comment: Should cases related to falsified medicinal products automatically be treated as serious, or does it still depend on the actual AE (if any) experienced?
Lines 957- 960		Comment: In what situation would a lawsuit not be implying causality from the primary source?
lines 974-975		Comment: this should be re-worded to "non-serious valid spontaneous ICSRs shall be reported by competent authorities in Member States or by Marketing Authorisation Holders after the interim period within 90 days from the date of receipt of these reports". This will exclude reports from post-marketing studies which are reported with the final study report/PSUR, and

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		it will make this chapter consistent with Annex 3.1., which does not require expedited reporting of non-serious cases during the interim period.
Lines 987-992		Today the industry faces the problem that many non-sense and bad quality reports are received (by the authorities and distributed by them - e.g. by the MHRA). The EGA is concerned that without a quality check at receipt (also medical) by the Agency such reports will be misleading when published to patients and consumers. The review described in 1527-1529 seems to be only a formal review.
Lines 1775-1778		Comment: Regarding the potential copyright issues affecting the handling of electronic copies of published articles, more protection to marketing authorisation holders is needed, as the use of these copies is performed to fulfil a legal obligation. Proposed change (if any): We propose to exclude the copyrights from those copies of published articles that are managed in order to comply with Good Pharmacovigilance Practices.

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SCIENCE MEDICINES HEALTH

18-April-2012

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

Comments from:

Name of organisation or individual
The European Pharmacovigilance Working Group (EPVWG)
The EPVWG has been in existence for more than 12 years and consists of 19 PV experts from both regulatory agency and broad industry backgrounds. During the past couple of years, the members of this Group have closely followed and participated in the development of the new PV legislation, directly as company representatives and/or indirectly through professional associations and networks. The EUPVWG welcomes the new legislation with its goals of simplification and harmonization of the EU PV legislation in order to better protect public health. The following comments on the draft GPV modules have been prepared by the Group and are focused on key areas for clarification or improvement**.**

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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Comment 1: There are definitions provided in section VI A 2.2 of instances of use of a product outside the terms of the marketing authorisation. It would appear that prescribing of a product by a HCP to his or her patient outside the terms of the marketing authorisation does not fall within any of the terms "overdose", "misuse" "abuse" or "medication error", but is another instance of use outside the terms of the marketing authorisation. It is not clear in this Module whether/when these different categorisations of such use must be specified for any reporting or other PV purposes.
	Recommendation regarding Comment 1: Provide clarification on both points raised in Comment 1 in the Module.
	Comment 2: In relation to receipt of ADR data by third parties with whom the Marketing Authorisation Holder has concluded a commercial agreement (lines 726 -735), the Module states that the Marketing Authorisation Holder "shall ensure" that the data are brought to its attention by such companies. It is also stated that the clock for expedited reporting by the Marketing Authorisation Holder starts when the third party receives the relevant information. This would appear to be irrespective of receipt by the Marketing Authorisation Holder. This statement is not supported by the wording of the legislation (Article 107.3, Directive 2001/83/EU as amended). The Module does not spell out what is expected of a Marketing Authorisation Holder by way of best practice in such a situation.
	Recommendation regarding Comment 2: Clarification of what steps a Marketing Authorisation Holder is expected to take vis a vis third parties in order to seek to ensure timely transmission of ADRs data. It is proposed that these would include the careful selection of contract parties, inclusion of appropriate contract terms, monitoring of compliance and taking action on the event of failures to comply with contractual terms. Other than through these mechanisms, a Marketing Authorisation Holder does not have the power to "ensure" the conduct of a third party company with which there is no constitutional link.

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 726-735		Comment: Clarification of what steps a Marketing Authorisation Holder is expected to take vis a vis third parties in order to seek to ensure timely transmission of ADRs data Proposed change (if any): It is proposed that these would include the careful selection of contract parties, inclusion of appropriate contract terms, monitoring of compliance and taking action on the event of failures to comply with contractual terms. Other than through these mechanisms, a Marketing Authorisation Holder does not have the power to "ensure" the conduct of a third party company with which there is no constitutional link.

Please add more rows if needed.

EphMRA

European Pharmaceutical Market Research Association
(EphMRA www.ephmra.org)

RESPONSE TO

Guideline on good pharmacovigilance practices: Module VI Management and reporting of adverse reactions to medicinal products

EMA/873138/2011

Introduction

The European Pharmaceutical Market Research Association (EphMRA) is an industry association representing those engaged in multi-country healthcare market research in Europe.

EphMRA is a well established organisation - 50 years old this year, widely known and respected in its field.

Member companies are made up of:

- Pharmaceutical manufacturers (38 members - the majority of whom are actively involved in research and development) who regularly conduct multinational market research and operate an international market-research function.
- Market research suppliers/agencies most of whom specialise in the healthcare field (154 members).

The purpose of EphMRA is to develop and improve standards and techniques in Europe for market research in the field of health and healthcare, and to strengthen the role of the Association in the relevant decision-making processes in order to support its members in their international activities and to create transparency to the general benefit. EphMRA's Code of Conduct, developed in conjunction with EFPIA is designed to safeguard the rights of respondents and protect data integrity. It provides comprehensive ethical and legal guidance for those involved in healthcare market research.

EphMRA also recognises that market research can perform a useful role when it comes to pharmacovigilance. EphMRA's Code of Conduct states:

> *"EphMRA is in complete support of the need to ensure that patients taking a pharmaceutical product are safeguarded from any short or long term adverse effects that could compromise their well-being. EphMRA supports the pharmaceutical companies need to comply with the policies set out by the authorities to try to ensure that any adverse events are reported to the appropriate manufacturer."*

Consequently EphMRA considers itself a stakeholder association with regard to the consultation process.

EphMRA

Background on market research

> *Market research is the systematic gathering and interpretation of information about individuals or organisations using the statistical and analytical methods and techniques of the applied social sciences to gain insight or support decision making. The identity of respondents will not be revealed to the user of the information without explicit consent and no sales approach will be made to them as a direct result of their having provided information.*
>
> *ICC/ESOMAR International Code 2007*

Typically market research projects are commissioned by pharmaceutical companies to be conducted by independent market research agencies. There are two different types of market research:

1. Ad hoc market research is designed and paid for by just one client company or marketing authorisation holder, the study is exclusive and unique to the commissioning company, who own the resulting data.

2. Syndicated market research is shared – both the findings and the costs - by a number of clients, however the data is owned by the market research agency.

   Syndicated data may or may not include longitudinal data i.e. repeated observations of the same items collected over a period of time, the population remains constant, the sample may or may not be the same.

Within the different types of market research one of two broad approaches can be taken:

- ☐ Qualitative – market research relying on open questions to explore the opinions and value judgements of individuals and from which collective general conclusions can be drawn.
- ☐ Quantitative – measurable data is gathered via closed questions from a representative sample. A profile of the population can be extrapolated from this data.

Each of these two approaches can be carried out using a variety of different mediums – face to face, on the telephone, online, through social media and via observation. Sometimes an interviewer is involved in the process and sometimes the market research is a self-completion exercise carried out independently.

EphMRA

General comments and questions

The issues and questions raised next relate to the reporting of adverse reactions from market research studies and reflect current concerns and confusion. EphMRA very much welcomes the opportunity the consultation process offers to clarify the role of market research in the forwarding of adverse reactions.

Query - List of Studies

VI.C.2.2.2. Solicited reports

Marketing authorisation holders shall record all reports of suspected adverse reactions originating from within or outside the EU, which occur in post-authorisation studies [DIR Art 107(1)]. In the context of this module, these solicited reports are those derived from organised data collection schemes initiated, managed, or financed by marketing authorisation holders and that do not fall under the scope of the clinical trials Directive 2001/20/EC. They include non-interventional post-authorisation studies, compassionate uses, named patient uses, other patient support and disease management programmes, registries, surveys of patients or healthcare providers, and information gathering on efficacy or patient compliance.

And

VI.C.2.2.2.1. Reports from non-interventional studies

Non-interventional studies should be distinguished between those with primary data collection directly from patients and healthcare professionals, and study designs which are based on secondary use of data such as studies based on medical chart reviews or electronic health care records, systematic reviews or meta-analyses.

Only reports of adverse reactions where a possible causal relationship with the suspected medicinal product is considered by the primary source or the marketing authorisation holder should be reported; other reports of events should be included in the final study report.

- For non-interventional studies with primary data collection directly from patients and healthcare professionals, only reports of adverse reactions suspected to be related to the studied medicinal product by the primary source or the marketing authorisation holder should be reported. Other reports of adverse reactions, suspected to be related only to medicinal products which are not subject to the scope of the study, and where there is no interaction with the studied medicinal product(s), should be reported to the concerned competent authorities where applicable by the investigators.
- For non-interventional study designs which are based on secondary use of data, adverse reactions reporting is not required. All adverse events/reactions should be summarised in the final study report

EphMRA emphasises that market research is not designed as a pharmacovigilance activity and is not included in the activities of pharmacovigilance. Market research is not a clinical activity either and market research studies should not be included within post-authorisation and non-international studies.

The collection of adverse events during market research studies is incidental and the function of market research studies is to enable market understanding and not to meet clinical needs as referenced above in the 'Background on market research'.

An established definition of market research is:

> Market research is the systematic gathering and interpretation of information about individuals or organisations using the statistical and analytical methods and techniques of the applied social sciences to gain insight or support decision making. The identity of respondents will not be revealed to the user of the information without explicit consent and no sales approach will be made to them as a direct result of their having provided information.
> *Definition of market research contained in the ICC/ESOMAR International Code 2007*

Information arising from market research studies is used internally by the pharmaceutical company and is part of business intelligence functions. Results are not published externally and no Health Authority/Ethics Committee approval is needed in the country where the market research study is being conducted.

Contact Information

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

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

Comments from:

Name of organisation or individual
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The line-numbering is not the same comparing published document of this Module under the EMA homepage with published document of this Module sent before. It could be a deviation of 1 or 2 lines.

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 195 - 196		**Comment**: It is stated that the primary source of the information on a suspected adverse reaction(s) is the person who provides information about the case. According to ICH-E2B the person is not reporting the case but the facts (ICH-E2B: line 362 – 363). **Proposed change (if any):** The sentence should be changed to: "The primary source of the information on a suspected adverse reaction(s) is the person who provides information about the ~~case~~ **facts**".
Line 211 - 213		**Comment**: Should reports coming from friends and relatives of medically qualified people really be managed as coming from a HCP if there is no evidence that the medically qualified person provided any input in the report?
Line 280 - 282		**Comment**: Definition of criteria for journal selection would be beneficial (e.g. impact factor, advisory board, other)
Line 289-299		**Comment**: If a company never commercialized the medicinal product in a country, why should a publication be considered by the concerned MAH? **Proposed change (if any):** Delete the sentence.

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 307 - 308		**Comments**: It is stated that marketing authorization holders should regularly screen internet or digital media under their management or responsibility, for potential reports of suspected adverse reactions. **Proposed change (if any):** It is suggested to change the sentence as follows: "Marketing authorisation holders should regularly screen internet **or company sponsored** digital media under their management or responsibility, for potential reports of suspected adverse reactions".
Line 313 - 325		**Comment**: Recommendation to screen internet sites of patients, to handle unsolicited reports as spontaneous reports and to verify the contact details – this is not feasible. In those internet sites the patients' privacy should be protected. A MAH should not contact a patient on those internet sites. All patients will be informed via the new PILs to report adverse side effects e.g. electronically to authorities. Registering of unsolicited cases is not reasonable. Registering of email-addresses without active reporting of the patient to the MAH and without permission of the patient contravenes data protection. **Proposed change (if any):** Delete the passage.
Line 326 - 328		**Comment**: If it does not qualify for expedited reporting, which action is proposed?

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): Describe the action proposed.
Line 514 - 520		**Comment**: How should that be realized (specially for unauthorized populations)? Why is a differentiation made with regards to unauthorized populations, while AR definition makes no reference to in label use anymore.
Line 542 - 551		**Comment**: Lack of efficacy is not applicable in cancer chemotherapy. E.g. if an antineoplastic drug has a rate of complete or partial remission of 20% this means, that 80% will have a progression or stable disease. It is not reasonable to register the 80% of cases as case of lack of efficacy. **Proposed change (if any):** Insert: "in cancer therapy, stable disease or progression of disease should normally not be classified as lack of efficacy."
Line 761 - 783		**Comment**: In oncologic and rheumatologic NIS, it would be an extensive workload and not useful to send non-serious cases from these NIS expeditedly in 90 days. E.g. hundreds and thousands of cases with nausea, fatigue, etc. Which exceptions could be made? Will it from already initiated NIS also be obligatory to send those cases expeditedly or does it only apply for new NIS beginning after July 2012? **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')*
		Delete requirement to send non-serious cases from NIS in 90 days.
Line 766 – 768 Line 776 - 778		**Comment**: It is mentioned that such reports shall be included in the CSR. We feel it should also be mentioned to include it in the PSUR.
Line 951		**Comment**: According to the definition mentioned in section VI.B.1.1. (unsolicited reports) and VI.B.1.2. (solicited reports) a report may be only solicited or unsolicited. Thus "stimulated unsolicited reports" are not defined. Proposed change (if any): The term "stimulated unsolicited reports" needs to be changed to "solicited reports": "Reports arising from class action lawsuits should be managed as ~~stimulated un~~solicited reports" or a new definition for "stimulated unsolicited reports" is needed.
Line 1022 - 1023		**Comment**: It is stated that competent authorities in Member States shall submit all serious ICSRs that occur in their territory to the EudraVigilance database. But in Directive 2010/84/EU Article 107a it is mentioned that each Member State shall record all suspected adverse reactions that occur in its territory which are brought to its attention from healthcare professionals and patients ... and should submit the reports electronically to the Eudravigilance database. **Proposed change (if any):**

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		It is recommended to be in line with the wording provided in the directive 2010/84/EU: "Competent authorities in Member States shall submit all serious ICSRs that occur in their territory and **which are brought to their attention from healthcare professionals and patients** to the EudraVigilance database."
Line 1095 - 1097		**Comment**: What is about other unsolicited reports, beside spontaneous? Would unsolicited not be more appropriate - instead of spontaneous?
Page 1578 **Table VI.1.** Process description - Identification of biological medicinal products. Step 2		**Reference:** Are batch number, brand name & active substance all present and identifiable? If Yes, create the case and send it to the correct receiver (step 3). If there is more than one batch number, structure the batch number that coincided with the adverse reaction in the Drug section (ICH-E2B (R2) B.4) and enter the other batch numbers in the case MAH/NCA

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')*
		narrative. If No, create the case and send it to the correct receiver (step 3) and follow-up with the reporter (step 2.1). **Comment:** B.4.k.3 allows for multiple batch lot number each separated by the delimiter defined by the transmission chosen. There is a character limitation of 35 Alpha-Numeric. Multiple batch numbers can be all structured and the batch number that coincides with the adverse reaction should be the first of the concatenation. **Proposed change (if any):** Step 2 description should be reworded as follows: If Yes, create the case and send it to the correct receiver (step 3). If there is more than one batch number, structure first the batch number that coincided with the adverse reaction in the Drug section (ICH-E2B (R2) B.4) followed by the other batch numbers. If No, create the case and send it to the correct receiver (step 3) and follow-up with the reporter (step 2.1).

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')*
Line 1723 - 1723		**Comment**: It is mentioned that articles can be excluded from reporting by the marketing authorization holder if another company's branded medicinal product is the suspected medicinal product. In the absence of a specified medicinal product source and/or invented name, ownership of the medicinal product should be assumed for articles about an active substance. Alternative reasons for exclusion of a published article are a specified formulation or a route of administration that is not consistent with the marketing authorization holder's medicinal product presentation. On the other hand in section VI.C.2.2.3. (line 829 – 832) it is stated: "Where ownership of the medicinal product by the marketing authorization holder can be excluded on the basis of the active substance name, formulation, route of administration, primary **source country or country of origin** of the suspected adverse reaction, the ICSR should not be reported to the competent authorities in Member States, or to the EudraVigilance database. Proposed change (if any): The "source country or country of origin" should also be mentioned in section VI.App2.6., line 1723 – 1723.
Line 1814		**Comment:** Table VI.3 The order of the sections 3 and 3.1 should be changed. It seems to be more appropriate first to check whether the case is serious and then whether the case is from EU. See also line 1839, Table VI.6 "final arrangements".

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<17 April 2012>

Submission of general comments on 'Good pharmacovigilance practices (GVP)'

Comments from:

Name of organisation or individual
EuropaBio [redacted], Manager, Healthcare Biotechnology [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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	EuropaBio, the European Association of Biotechnology Industries, thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the first wave of draft GVP modules. EuropaBio's mission is to promote an innovative and dynamic biotechnology based industry in Europe. EuropaBio, has 62 corporate and 7 associate members operating worldwide, 2 Bioregions and 19 national biotechnology associations representing some 1800 small and medium-sized enterprises. EuropaBio broadly supports the comments provided by EFPIA, the European Federation of Pharmaceutical Industries and Associations, and would like to provide some additional general comments of specific importance to its members. Our comments focus on important aspects related to the expected business impact for small and medium-sized enterprises, as well as to advanced therapy medicinal products. EuropaBio welcomes the alignment with existing ATMP-specific guidance (e.g. guideline on safety and efficacy follow-up – Risk management of ATMPs – EMEA/149995/2008), which brings a certain level of stability in the legal framework for companies operating in the field.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	We would like to highlight that specifically for SMEs adequate transitional periods and proportionate implementation of the significant system changes are necessary while avoiding unnecessary administrative burden.	
Module II PSMF – Transition from the DDPS	We strongly welcome the introduction of the PSMF independent from a specific marketing authorisation and we recommend a simple and pragmatic transition process for products with existing DDPS. As a PSMF is required for any new MAA and for all renewals due after the implementation date, we believe that many MAHs would have an interest in moving to PSMF for all authorised products at once to avoid maintaining both a PSMF and a DDPS in parallel as well as reducing the number of variations to be submitted. The change-over is currently proposed to occur for each product including a DDPS via a Type IB Variation. In order to reduce administrative burden for Industry and Regulators, we recommend using a Type IB worksharing procedure per group of MAHs sharing the same PSMF and including a list of all affected products authorised in the EEA regardless of their specific registration route covering one Type IB fee. We strongly encourage the national competent authorities to immediately implement the outcome of the worksharing procedure into all national authorisations without any further national process. This will ensure a	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	consistent and pragmatic phasing in of the new PSMF across EEA without unnecessary administrative burden. The management of changes to the PSMF should completely be delinked from the Variation regulation and any specific MAAs. The summary of the PSMF covering location and contact details of the EU QPPV person should solely be managed through notification of required updates to the EVMPD and not trigger any variation process.	
Module II PSMF – Co-licensing/Co-marketing scope	The scope of description and documentation of co-licensing and co-marketing arrangements in the PSMF is unclear. However, the expectations for inspections need to be explicit. Within the current Volume 9A it has until now been applicable to arrangements within the EEA. Please clarify that the scope is being limited to commercial arrangements applicable to markets within the European Economic Area.	
Module V RMP – ATMP section	Duration of exposure to the medicinal product may be a challenging subject to describe for ATMPs, as the kinetics of cells and genes are different as compared to classical molecules. E.g. Manipulated cells can be used in a single administration to initiate a biological repair process. It is however unknown what proportion of these cells will actually become an intrinsic component of the repair tissue and for how long these cells will be retained. Please specify how exposure duration should be calculated and how relevant is this parameter is in such	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	case.	
Module V RMP vs Module VII PSUR - document structure and interchangeable modules	The scope and purpose of PSUR and RMP are not always clear, because of the focus and the overlap in some modules of both documents. Although the PSUR is considered to be mainly used for post-authorisation information reporting, it is also expected to capture pre-market experience. This applies vice versa to the RMP where post-authorisation data are reported. We propose to clarify and simplify both document purposes and structures. The RMP should focus on the pre-authorisation strategy including the binding commitments for post-authorisation development, while the PSUR should focus on the post-authorisation phase reporting the results or the development activity and monitoring of the adverse events. Emerging post-authorisation data should not require updating of both documents, but rather require only one document update. A specific section for risks associated with a Medical Device is necessary for the use of Drug Delivery Systems and better linkage with the Risk Management Systems of such devices that follow different methodologies. For the sake of clarity, we propose that all post-authorisation studies, whether they are PASS or	

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	PAES, are included into one Annex to the RMP. Both study types usually include safety parameters and may not easily be distinguishable. The significant expansion of the RMP content and the administrative burden of producing an updated RMP document should be taken into account by the Regulators. We discourage establishing a practice of "routine" updates to an RMP in the absence of any new information that materially affects the product's benefit-risk balance and, consequently, the absence of any need for modifications to the pharmacovigilance and risk minimisation activities.	
Module V RMP – comprehensive review process including local inputs	A comprehensive process to include additional national risk minimisation activities or drug utilisation studies within the RMP needs to be thought through in detail as multiple ongoing parallel discussions in the post-authorisation phase might unnecessarily slow down market access for innovative products and can prove to be especially challenging for SMEs. The PRAC is responsible for assessing the overall RMP and as such involves representatives from all Member States. We recommend that this process should ensure that any specific local requirements are included during the PRAC assessment process. In addition, drug utilisation studies to be recorded within the RMP should be strictly limited to the EEA region.	
Module V RMP and	The schedule for submissions of RMP updates is not well	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
Module VII PSUR – submission schedule for updates and document life-cycle management	defined, and may differ from the schedule for submission of PSURs. The data intervals under review may therefore differ between the 2 documents, limiting the "interchangeability" of the overlapping content. A clear co-ordination and document life-cycle management process needs to be established for both documents to maximise their value and avoid any confusion or redundancy. To ensure consistency, the same rapporteur should be utilised for the assessment of PSURs and RMPs as well as any product related PASS. The assessment process for PSURs may last beyond 6 months. This will pose challenges for products requiring very short PSUR submission cycles and taking into account the data lock points and adequate time to analyse and prepare the following PSURs. We strongly welcome the new proposal that any changes recommended as a consequence of a PSUR review are implemented into the product information without any subsequent variation submissions.	
Module VI ICSR - webmonitoring	In support of a proportionate implementation of the new requirements, we propose that the monitoring of ICSRs from websites should be focused on company-sponsored sites. Active screening of non-sponsored websites for adverse reactions is a resource consuming and challenging task, especially for SMEs. In addition, the scientific validity of such sources is often not quantifiable. The added value of such reports over	

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	scientific publications is questioned in relation to the additional effort required to capture, analyse and assess the information from blogs, forums, etc.	
Module VI ICSR – Validation of reports	Under the new requirements patient or consumer reports should be handled as spontaneous reports irrespective of any subsequent 'medical conformation'. The only requirement for a reporter to be considered identifiable is the availability of contact details in order to confirm or follow-up the case. We are concerned that a MAH or Regulatory Agency may not be able to distinguish genuine, authentic adverse reactions reported by a patient/consumer from fake reports that may have been submitted under a fake email address (identifiable reporter with contact details). Some clarification regarding the confirmation of the existence of a reporter needs to be established.	
Transitional periods	As a general rule, new processes or templates should become mandatory for use 6 months after they have been finalised to allow companies adapting their internal processes and documents. Changes involving adaptations to IT systems should be phased in with at least 18 month transitional periods as significant re-programming, validation and company investment are required for their implementation.	

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Comments from:

Name of organisation or individual
European Organisation for Rare Diseases

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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')*
161-164		Comment: A patient may have taken the recommended dose, but due to his/her metabolism, or due to interaction, the drug accumulates above the desired concentrations. Overdose could include over-exposure, not due to too high dose taken compared to recommended dose, but due to a too high dose taken given the patient metabolism profile or interaction. Proposed change (if any): Adapt definition or revise the paragraph name to "over-exposure"
310-316		Comment: Digital media is considered company sponsored if it is owned, paid for or controlled by the MAH… And the footnote says a donation to an organisation/site by a marketing authorisation holder does not constitute ownership. When a donation is made for the purpose of developing the digital media, then the process by which the site is paid for falls under "considered as company sponsored". To avoid this confusion, it should be clear that the donation should be unrestricted. Proposed change (if any): Footnote 7: A donation (financial or otherwise) to an organisation/site by a marketing authorisation holder does not constitute ownership, provided that the marketing authorisation holder does not control the final content of the site and provided the donation is fully unrestricted and given without return consideration.
317-321		Comment: As the European Commission is proposing a comprehensive reform of the data protection rules (http://ec.europa.eu/justice/newsroom/data-protection/news/120125_en.htm), in particular for citizens receiving medical treatment, it may not be recommended for MAH to "actively monitor digital media or sites

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')*
		such as those of patients' support or special disease groups". Discussions between patients are discussions between patients, to the exclusion of third parties, in full respect of confidentiality and privacy protection. MAH are not expected to directly participate in these discussions. Accordingly, "active monitoring" should not consist of a direct interaction with the patients registered in the digital media (be the media closed or open), or a query into archived messages, at most a request to the person in charge of the media/site to analyse what is said about medicines in question and possibly feedback the MAH about any information of interest for pharmacovigilance purposes, provided that users of the media have given their agreement. Proposed change (if any): It is also recommended that the marketing authorisation holder actively contacts the administrators of special internet sites or digital media such as those of patients' support or special diseases groups in order to check if they describe significant safety issues which may necessitate reporting in accordance with the recommendations described in VI.C.2.2.6. In case patients' discussions are investigated, it should be done in full respect of the site/media operation guidelines and privacy protection, with the information and consent of the patients. When the social media is public domain (e.g. open forum), the marketing authorisation holder that is monitoring the information should inform the administrator of the social media that it does so.
679-685		Comment: "All appropriate measures": such as? If no more precise guidance, then risk of large disparities across Member States. We would like to contribute to the definition of some that seem most relevant, practical and effective. Proposed change: Each Member State shall take all appropriate measures to encourage healthcare professionals and patients or consumers in their territory to report suspected adverse reactions to their competent authority. Eligible patients', consumers' and healthcare professionals' organisations will be consulted on the definition of proposed measures that would be practical, efficient and appropriate to encourage their respective

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')*
		constituencies to report.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 17th, 2012

Submission of comments on 'GVP Module VI – Management & Reporting of ADRs (EMA/873138/2011)

Comments from:

EVM
EVM welcomes the opportunity to comment on the public consultation of the first batch of modules on good pharmacovigilance practices (GVP). EVM would like to point out that some of the vaccine specificities addressed in the guideline on the conduct of pharmacovigilance for vaccines for pre- and post-exposure prophylaxis against infectious diseases (EMEA/CHMP/PHVWP/503449/2007) have not been incorporated into the new PV modules. In this respect, the EVM would like to stress the need to clarify whether the above-mentioned guidance will be incorporated into the Pharmacovigilance Modules (GVP) or remain a separate effective document.

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Several key terms and phrasings are used inconsistently in the Modules. This is unnecessary and can lead to difficulties in correct and easy understanding. All this is easily avoidable by establishing the consistency. As the Modules will be in use for years, now is the only moment to do it. Examples of inconsistencies are provided in the specific comments below as editorial 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')*
Lines 364-370		Comment: Please clarify if the invalid ICSR reports should be captured in the MAH database
Line 479		Comment: Please clarify what is meant by " long half-life"
Line 498		Comment: Please clarify if the wording "Termination of pregnancy" includes all pregnancy outcomes or only abortion. Proposed change: Please add a definition for "Termination of pregnancy" in Annex I.
Lines 498-501		Comment: Should these cases be considered systematically as serious? And does it include report with and without adverse events?
Line 518		Comment: The term "use of a medicinal product in an unauthorised population" (line 518) appears to refer to off-label use. Off-label use is however not defined. Proposed change: Should the term concerned refer to off-label use, it is proposed to mention this at least in brackets and define off-label use in Annex I. Should the term concerned refer to something else, this should be explained.
Lines 536-555		Comment: This section provides guidance for regulatory reporting of **"Lack of therapeutic efficacy".** The section concerned emphasizes the regulatory reporting of lack of efficacy of vaccines. However, a definition is neither included in Annex I nor referred to. Similarly, lack of efficacy is not included in the definitions in Module VI, section VI.A.2.1.2. Proposed change:

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')*
		CIOMS/WHO has recently issued a professional and well structured guidance lack of efficacy of vaccines ("Definition and Application of Terms for vaccine Pharmacovigilance, 2012, section 3.2 **"Vaccination failure"**). It is strongly proposed to take this international recommendation into consideration in Module VI. The CIOMS/WHO document clearly sees the lack of efficacy of vaccines as a considerably more complicated issue than that of other medicinal products. Furthermore, it sees vaccine-specific aspects as the solution to address lack of efficacy of vaccines adequately.
Lines 550-555		Comment: Do cases reported as lack of therapeutic efficacy / vaccination failure have to be confirmed by biological proofs in order to consider them as lack of therapeutic efficacy reports and as valid reports? Proposed change: It is suggested to define what should be considered as a lack of therapeutic efficacy in Module VI. A.2. Definitions
Lines 822-830		Comment: Please clarify whether the "Lists of scientific and medical literature and active substances names" will be available on the agency's website.
Lines 993-1041		Comment: Lack of therapeutic efficacy for vaccines, even if non-serious, should be considered as expedited within 15CD (refer to VI.C.6.2.3.4 – line 1444). Proposed change: Need to specify how and to whom non-serious lack of therapeutic efficacy with vaccines should be reported during the interim arrangement.
Lines 993-997 & 1019-1023		Comment: As these chapters do not cover all situations (e.g. non-serious lack of therapeutic efficacy with vaccines) the wording needs to be adapted Proposed change: Add the words in italic

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')*
		l. 996 - "...the following *general* reporting requirements shall apply to healthcare professionals and non-healthcare professionals valid ICSRs" l. 1021 – "... the following *general* requirements, detailed in Articles 107(3) and 107a(4) of Directive 2001/83/EC..."
Line 1396		Comment: Please specify the gestation dates for which a miscarriage or "early spontaneous abortion" is applicable
Line 1827		Comment: Need to specify that this table VI.4 refers to general expedited reporting requirements as it does not deal with all the situations (e.g. Lack of therapeutic efficacy for vaccines, even if non-serious, should be considered as expedited within 15CD) Proposed change: Add the words in italic "Table VI.4. *General* expedited reporting requirements"
Line 1844		Comment: Need to specify that this table VI.7 refers to general expedited reporting requirements as it does not deal with all the situations (e.g. Lack of therapeutic efficacy for vaccines, even if non-serious, should be considered as expedited within 15CD) Proposed change: Add the words in italic "Table VI.7. *General* expedited reporting requirements"
EDITORIAL COMMENTS		
Lines 150-151 and lines 210-211		Comment: There appears to be an confusing and unnecessary inconsistency regarding the use of key phrasings: **"...causal relationship between a medicinal product and an adverse event"** e.g. lines 150-151) **and "causal relationship between a medicinal product and the reported adverse reaction**,..." (e.g. lines

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')*
		210-211). Proposed change: It is proposed to use adverse event instead of adverse reaction. Should the mentioned example intend to have different meanings, this should be explained. Otherwise consistency is proposed.
Lines 206-207, 199-200, 212, lines 215, 238, 240, 267, 272, 769, 775, 802, 811, 817		Comment: Consumer is clearly defined **"as a person who is not a healthcare professional such as a patient…"** (e.g. lines 206-207, 769, 775). It appears therefore unnecessary to use the hybrid phrasing **"consumer or patient"** (e.g. lines 199-200, 212, 354 and throughout at least Module VI). Furthermore, the hybrid phrasing **"consumer or patient"** as well as the terms **"consumer"** or **"patient"** are used in a confusing and unnecessarily inconsistent way throughout at least Module VI (e.g. lines 215, 238, 240, 267, 272, 769, 775, 802, 811, 817). Proposed change: Consistency is proposed using this wording
Lines 289, 822-823, 863		Comment: The phrasing "…and **record ICSRs** related to medicinal products **issued** from spontaneous **reports** or non-interventional studies" appears unclear. In particular the bolded words require more clarity. What is exactly intended with Record… … ICSRs"? When spelling out "ICSRs" one has the phrasing "Individual **Case Safety Reports related to… … spontaneous reports"**. This appears tautologous and is difficult to understand. The same tautology appears e.g. on lines 822-823, 863). Does "issued" mean "originating"?
Lines 254, 398		Comment: The phrasings **"clinical assessment"** (e.g. line 254)

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')*
		and **"scientific evaluation"** (e.g. line 398) appear to be used interchangeably. For the use of different phrasings there is no reason as long as the same is intended. Proposed change: It is proposed to use the phrase **"clinical assessment"** consistently throughout the text. In the unlikely case that the two example phrasings are intended to have a different meaning, this must be explained.
Lines 243-244, 247		Comment: The phrasings **"...collection of ... ...suspected adverse reactions"** (e.g. lines 243-244, 725, 728, 748) and **"collection of reports"** (e.g. lines 247, 249, 720, 730-731, 751) appear to be used interchangeably. Proposed change: It is more logical to use the latter phrasing **"collection of reports"** as a report stands for something tangible and therefore collectable, unlike a reaction which is not tangible. As a minimum, the selected term should be used consistently.
Lines 268, 335, 343, 347		Comment: The phrasings **"organised data collection schemes"** (e.g. line 268) and **"organised data collection systems"** (e.g. lines 335, 343, 347) appear to be used in an interchangeable way. Proposed change: It is proposed to select one phrasing and use it consistently.
Lines 261, 322, 260, 334, 340, 750		Comment: The phrasings **"solicited/unsolicited source"** (e.g. line 261), **"solicited/unsolicited case"** (e.g. line 322) and **"solicited/unsolicited report"** (e.g. lines 260, 334, 340, 750) appear to be used interchangeably. Proposed change:

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')*
		It is proposed to select the latter phrasing "**solicited/unsolicited report"** and use it consistently.
Lines 337, 354, 264, 335 414		Comment: The phrasings **"healthcare provider"** (e.g. line 337), **"health professional"** (e.g. lines 354) and **"healthcare professional"** (e.g. lines 264, 335, 414 appear to be used in an interchangeable way. Proposed change: It is proposed to select the latter phrasing **"healthcare professional"** and use it consistently.
Line 1854		**"ICSRs**" instead of **"icsrs".**

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18/04/12

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

Comments from:

Name of organisation or individual
Faculty of Pharmaceutical Medicine

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1. General comments

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

2. Specific comments on text – P&G

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 5 line 158 and page 12 line 366		Comment: Page 5 line 158 – this refers to events being unrelated to the medicinal product while on page 12 line 366 it refers to events being excluded – is this consistent? Proposed change (if any): Ensure consistency
Page 6 line 189		Comment: Use of "Since" is confusing at the start of the sentence Proposed change (if any): or trade names of the medicinal product. A medicinal product is authorised with a defined
287 – 290		Comment: ICRS are to be identified from the literatures, but it is not clear if this means all ADRs, whether or not serious/non-serious or unexpected/expected. Proposed change (if any): Please clarify if all ADRs including non-serious expected ADRs should be recorded in the MAH's database.
291 – 295		Comment: The statement regarding reports in the literature from a country where the MAH has never commercialised the product is unclear. Proposed change (if any): Please clarify here that the MAH can ignore such reports as far as expediting cases is required, as indicated in lines 835 to 838.
Page 10 line 293		Comment: "This also applies.." use of these words is confusing

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): Reword
384 - 387		Comment: If an HCP cannot downgrade a consumer report to Not-related, there does not seem to be any point in asking for medical confirmation of a case in future (lines 412-416), since the case will be expedited regardless, based on assumed causality as per lines 155 & 156. Proposed change (if any): Please clarify why medical confirmation is still required.
Page 22 line 740		Comment: could you clarify the word "concluded in this sentence? Proposed change (if any)
822 - 830		Comment: The MAH's role regarding publications monitored by the agency is unclear. Is the MAH still expected to review the same journals and add any case reports included in them to their database? Will the Agency inform them of any case reports identified during their monitoring? Proposed change (if any): Clarification on the MAHs role regarding such publications is required.
Page 25 paragraph starting at 843		Comment: does this mean if there is a literature report with a table that contains enough detail to qualify as a valid report, if it is serious it does not need reporting within 15 days? Proposed change (if any)
Page 25 line 845		Comment: surplus "s" after "article" Proposed change (if any): literature article describes adverse reactions, which occur in a group of patients with a designated
921 - 928		Comment: This section states that Emerging Safety Issues are to be reported forthwith / immediately. Since

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')*
		these include safety issues from Signal detection activity and urgent safety restrictions the reporting timelines are unclear. Proposed change (if any): It would be helpful if the timelines for reporting such issues were specified more clearly.
1044 - 1050		Comment: The Agency will report ADRs to WHO, but will WHO report cases to the Agency? Proposed change (if any):
1226 - 1227		Comment: Discretion is allowed for MedDRA coding of either the diagnosis alone, or the diagnosis plus its associated signs and symptoms. Proposed change (if any): This guidance should not allow for alternatives, but state which option should be followed, in order to ensure consistency of reporting between companies.
1289 - 1290		Comment: New information should be clearly identifiable in the case narrative. Proposed change (if any): Guidance should be provided as to how this should be achieved (e.g. leaving the original narrative as previously submitted and adding new information at the end).
1308 – 1310 1318 - 1321		Comment: 1308-1310 says the correction of typos does not require expedited reporting. However, 1318 – 1321 suggests that this can be done but without changing the date of receipt of the most recent information. Proposed change (if any): Please clarify this apparent contraindication.
1336 - 1345		Comment: Pseudonymisation may be used for names and addresses.

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): Please clarify exactly what is expected in these fields.
1407		Comment: This line and others in the guideline refer to the Implementing Measures. It is confusing to have two documents to describe the same processes. Proposed change (if any): Incorporate all relevant information from the Implementing Measures into this and other GVP guidelines, as applicable.
1442 – 1444		Comment: This section refers to expediting Non-serious cases of lack of efficacy. Should cases of lack of efficacy which are subject to 15 day reporting (e.g. for vaccines and contraceptives), not all be considered as medically important and thus serious cases? Proposed change (if any): Please clarify why these cases should not automatically be considered serious.
Page 26 section C.2.25		Comment: why has the transmission of an infectious agent been removed from the definition of serious but requires 15 day reporting? Proposed change (if any): clarification of the change
Page 40 – section 6.2.3.5		Comment: Why are the EMA dictating the LLTs that should be used for quality defects or falsified medicinal products Proposed change (if any): Allow MAHs to determine the most appropriate coding
Appendix 3		Comment: Appendices 3.1 and 3.2 are self-explanatory, but it is not clear when Appendix 3.3 should be followed. Proposed change (if any): Please clarify when the process in Appendix 3.3 is to be followed.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
Gilead Sciences International Limited

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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')*
161		Comment: The definition of overdose is confusing referring to quantity of product per day and latterly cumulative effects due to overdose.
284-286		Comment: Please clarify follow up expectations for literature reports.
313		Comment: Recommendation to monitor special internet sites or digital media such as support or disease groups to check if they describe significant safety issues which may necessitate reporting seems unnecessarily burdensome and should be limited to those sponsored by the MAH.
327		Comment: How is validity of an e-mail to be performed?
409		Comment: Follow up to outcome – why is this necessary as sometimes sufficient information exists without follow-up to outcome?
439		Comment: Please clarify the meaning of terminologies – is this MedDRA, database conventions or something else?
698-700		Comment: The MAH will have internal processes for follow up of reports it receives – what is the intent and role of the member state here?
792		Comment: No definition in VI.A.2.2 of compassionate use/named patient use. 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')*
		Include definition of compassionate use/named patient use in VI.A.2.2.
798		Comment: It is unclear how provision of drug for compassionate use with associated safety language letters of agreement requesting SAEs/SADRs etc to be reported could result in a compassionate use study where data is not solicited – please clarify.
811		Comment: As for 798, the example is weak as if the MAH PSP is to support prescription fills – certain safety language and training of personnel making such contacts would be expected?
1286		Comment: Please clarify that initial receive date never changes, only the date of receipt reflect follow up information.
1318 to 1324		Comment: Implies that for a corrected case that does not change the medical evaluation of a case, the clock start date should not be re-started, but for a corrected case that does change the medical evaluation. For example, a case incorrectly classified as non-serious is corrected to serious, then a new clock start date can be applied even if no new information has been received – is this correct?
1345		Comment: For risk management purposes ethnicity is also a key parameter which data protection groups are objecting to – guidance here would be appreciated.
1482		Comment: Please provide examples where data would not be sought in non-interventional organised data collection schemes – this is a possible area for confusion and lack of clarity.
1153		Comment: Please provide guidance on format.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
H. Lundbeck A/S

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1. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
General comment, page 5 line 143		Comment: Off label definition missing ("use outside the terms of marketing authorisation" equals off label…) Proposed change (if any):
Page 10 line 287		Comment: Does this mean that no literature AE reports where the author says causality not related, but the MAH disagrees should be considered as related AE reports? Proposed change (if any):
Page 23 line 766		Comment: "adverse reactions" Proposed change (if any): please change to "adverse events", since adverse reactions already states a causal relationship. Otherwise rewrite the whole sentence
Page 24 line 816-822		Comment: Any timelines for the implementation of the Agency literature review list?
Page 27 line 918		Comment: "Immediately" is time unspecific Proposed: Within xxx hours/working days?
Page 28 line 956		Comment: "exceptional circumstances" should be further specified (…cases from reports as Texas poison etc…)
Page 28 line 968		Comment: Non serious valid…should be rephrased, since MAH should only submit Non serious cases with EU origin expedited

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 33 line 1148		Comment: "immediately" Proposed: Within xxx hours/working days?
Page 35 line 1246		Comment: "..may comment". Does this mean that a causality statement by the MAH is not needed?
Page 37 line 1305		Comment: "medical judgement" should be defines. Is it judgement by af Health care professional, physician etc?
Page 39 line 1390-1395		Comment: Does this mean that the parent report should always be on the mother and only a statement is made that the medication was taken by the father? What about the coding of "exposure via father"

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

01 March 2012

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

Comments from:

Name of organisation or individual
Hal Allergy, The Netherlands

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The expedited reporting requirements applicable to MAH are with regards to all serious and/or non-serious ADRs. Is listedness a factor in a expedited reporting decision or all, listed and unlisted ADR should be reported?
	If non-interventional studies are considered as solicited reports and classified as study, does this mean that non-serious ADRs should not be collected and reported on expedited base in the safety database but described in the final study report?

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):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>
April 16th, 2012

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

Comments from:

Name of organisation or individual
International Plasma Fractionation Association (IPFA)

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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The new regulation is supposed to harmonise and simplify ICSR reporting within EU. In the transitional period would it be possible to have the information on all EU CA requirements available in a single point and not to be obliged to consult each individual national websites?

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')*
1369		Comment: Sometimes when a case is nullified it could be logically deleted in the sender's PV database (for example when it is the concerned product is of another MAH (ex 13 in appendix 5) since there is no reason to keep this case in the sender's database. Could you please clarify the sentence in line 1369? Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
Janssen Pharmaceutical Companies of Johnson & Johnson

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*).*

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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 128-130		**Comment:** In section VI.A.1. it is stated that the Scope of this Module regards the collection, data management and reporting of suspected adverse reactions with medicinal products for human use authorised in the EU. However, in section VI.A.2.2. (lines 185-188) it is stated that the scope of this module is not only applicable to medicinal products authorised in the EU but also to any such medicinal products commercialised outside the EU by the same marketing authorisation holder. This is an extension to what is stated in the general scope under section VI.A.1. **Proposed change (if any):** Propose to add the following to section VI.A.1 to improve consistency between sections. 'The Scope of this Module regards the collection, data management and reporting of suspected adverse reactions with medicinal products for human use authorised in the EU and to any such medicinal products commercialised outside the EU by the same marketing authorisation holder.' *(Cross-refer to section VI.A.2.2)*.
Lines 136-140		**Comment:** All definitions in VI.A.2.1 should be consistent with those provided in Annex I – Definitions and should cross-refer to that document
Lines 152-153		**Comment:** This just seems to repeat what has already been stated in lines 149-151, and is not really that helpful in differentiating the two terms **Proposed change (if any):** It would be more helpful to clearly define adverse event as well as adverse reaction so that the difference is

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')*
		clearly differentiated.
Lines 161-164		**Comment:** Definition of overdose requires clarity as insinuates objectivity. **Proposed change (if any):** Suggest clarifying "above maximal recommended dose according to the authorised product information" or adding examples on its meaning. E.g., if maximum dose is 40 mg (1 tablet) and patient receives 60 mg (1.5 tablets) is that an overdose? What if overdose section of label contains information that in studies of doses up to 100 mg found the drug to be safe?
Lines 170-178		**Comment:** As per misuse section, examples should be used for abuse, medication error and occupational exposure. **Proposed change (if any):** Clarification with examples for the above.
Lines 175-176		**Comment:** Definition for medication error is somewhat vague. **Proposed change (if any):** Suggest using The National Coordinating Council for Medication Error Reporting and Prevention definition of medication error - "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution;

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')*
		administration; education; monitoring; and use" and providing examples of types of medication errors should be captured by MAH.
Lines 177-178		**Comment:** Definition of accidental exposure (not associated with occupation) is missing. **Proposed change (if any):** Add section to describe above.
Line 212-216		**Comment:** In section VI.A.2.3. A report submitted by a medically qualified patient, friend or relative of the patient is to be considered as a healthcare professional report. Would clarify that this is then also to be considered as *'a spontaneous report confirmed by a healthcare professional.'* **Proposed change (if any):** Amend Line 214-216 to be consistent with lines 208-211: 'Similarly, if a report is submitted by a medically qualified patient, friend or relative of the patient, the case should also be considered as a spontaneous report confirmed by a healthcare professional.*'*
Line 246		**Comment:** Minor editorial note - hyperlink to Section VI.A links to line 241 (=end of section VI.A.2.5), whereas it should link directly to line 124 (=start of section VI.A). Hyperlink to Section VI.C links to line 607 (=end of section VI.B.8), whereas it should link directly to line 608 (=start of section VI.C). **Proposed change (if any):** Correct the hyperlinks throughout document.
Lines 298-299,		**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')*
843-844		Additional guidance is required in regard to identifiable patient and literature sources. If a literature article (not a safety summary, table or line listing per lines 843-844) describes a group of patients, e.g. 50 adult females, who experienced a particular adverse reaction (and no distinguishing feature), should 50 cases be created even though there is no ability to uniquely identify the patients? **Proposed change (if any):** Additional guidance is required on how to handle literature articles that describe a particular group of patients and a specific number is provided; however, there is no information that uniquely identifies the patients.
Line 313		**Comment:** Digital media may be paid for AND controlled by sponsor **Proposed change (if any):** Amend text to reflect this to '...if it is owned, paid for and /or controlled...'
Lines 317-320		**Comment:** This *recommendation* (insinuating this is NOT a requirement) is a significant change compared to requirements in Vol 9a. It would be very resource intensive to manage the identification and active monitoring of all relevant non-company sites and/or to establish validity/reliability of the information posted. We agree it can be a potentially useful tool to monitor trends, but further guidance may be useful as the use of internet sites continues to grow. **Proposed change (if any):** Ethics, transparency, and appropriate 'listening in' of non company sites have not been discussed but they are crucial aspects of monitoring digital media. This recommendation requires comprehensive guidance and in

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')*
		current state is insufficient to guide implementation of such recommended monitoring activities.
Lines 322-324		**Comment:** Examples of 'organised' digital systems should be used for when reports should be considered solicited. A pragmatic approach to obtain follow up information should also be described. **Proposed change (if any):** Examples of organised digital systems should be provided and the approach to obtain follow-up information explained.
Lines 327-328		**Comment:** Contact details to only be used for PV purposes. However data can be used for other purposes if consent is provided? **Proposed change (if any)**: Please clarify that contact can be used for other purposes if consent is provided.
Lines 328-329		**Comment:** 'If the country of the primary source is missing, the country where information was received should be used as the primary source country.' This statement can be confusing in an electronic environment as servers storing information may be in one country but the information may be accessed in another and can lead to inaccuracies in data collection. Also the website may be a .co.uk whilst someone accesses the information in another country. **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')*
		Please clarify what is meant by 'received' when referring to Digital Media and what is meant by 'depending where the review takes place.'
Line 330-332		**Comment:** We understand this sentence to mean that if an MAH simply becomes aware of a suspected adverse reaction on a non-company sponsored digital media (i.e. not through a routine monitoring activity such as recommended in lines 317-321) that such reports should be assessed in the same way as other spontaneous reports. **Proposed change (if any):** Amend the text to clarify this point further
Lines 361-362		**Comment:** 'an identifiable patient who ***may*** be characterised...' Does this mean that a report could still be considered valid if just 'a patient' (with no other identifier) is present? **Proposed change (if any):** Provide clarity on the minimum information required to consider a patient identifiable. Consider replacing 'may' with 'must'.
Lines 364-368		**Comment:** Some companies will consider causality for a spontaneous report to always be 'Possible', regardless of the reported causality, and will be retained as a valid report. It is unclear whether this 'implied causality' approach to spontaneous reports is being discouraged by this section. **Proposed change (if any)**: Please clarify whether a company can treat an ICSR as invalid if the reporter (whether or not medically qualified) has stated that a causal relationship can be excluded, as this conflicts with implied causality principle

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')*
		usually applied to spontaneous reports.
Lines 368-370		**Comment:** There is no mention of situations in which a MAH receives information about an outcome only with no details on the type of adverse reaction experienced, e.g. Patient died. Patient was hospitalized. We *assume* the same approach would be used. **Proposed change (if any):** Please address the above point including whether such information is reportable, and if it meets the 15 day reporting requirement
Lines 423-427		**Comment:** Additional detail is required on how to manage data received via digital media. What is considered to be primary source data? How should this be managed / stored appropriately? (E.g. Should the print screen function be used to create a screenshot?) **Proposed change (if any):** Additional clarification on the above.
Line 450		**Comment:** 'Databases should be reviewed regularly to identify and manage duplicate ICSRs'. No further guidance is provided on the management of duplicate ICSRs. **Proposed change (if any):** 'Define 'regularly' and provide additional guidance on how should this review be demonstrated?

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 527-528		**Comment:** As part of a RMP, these terms may require expedited reporting of ICSRs to certain HAs for selected products. So this exception should be stated here. **Proposed change (if any):** Amend text to state an exception to terms that may require expedited reporting according to RMPs. "Reports of overdose, abuse, misuse, medication error and occupational exposure with no associated adverse reaction should not be reported in an expedited manner as ICSRs, unless required as part of an RMP."
Line 536-549		**Comment:** In section VI.B.6.4. Lack of therapeutic efficacy it is stated that, in certain circumstances, reports of lack of therapeutic efficacy should be expedited as ICSRs within a 15 days' time frame. Medicinal products used for the treatment of life-threatening diseases, vaccines and contraceptives are examples of such cases. **Proposed changes (if any):** Clarify, as an example, whether emergence of resistance following antiretroviral treatment of HIV would be considered to be within scope of above.
Line 584		**Comment:** Regarding the 15 calendar day timeframe and starting when any personnel of the MAH becomes aware of a serious valid ICSR, it should be clarified that this is applicable to anyone working on behalf of MAH also such as consultants or contractors. **Proposed changes (if any):** Clarify that contractors and consultants are also included in the definition of MAH personnel.

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 715		**Comment:** Additional national obligations should not be imposed unless justifiable grounds. **Proposed changes (if any):** Define justifiable grounds by using examples should be given to clarify what is deemed justifiable and what is not justifiable grounds.
Line 747		**Comment:** 'May consider utilising their websites to facilitate the collection of suspected adverse reactions...' We assume this is a recommendation only and not a requirement. **Proposed changes (if any):** Confirm that this is not a mandatory requirement for the MAH and whether AEs collected as a result of this process should b considered 'spontaneous'.
Line 777-781		**Comment:** No mention if AEs for these other products are to be handled as solicited or spontaneous reports. How should the sponsor have oversight that the investigator is reporting this? **Proposed changes (if any):** Clarify how adverse reactions for other products in non-interventional studies should be classified (I.e. solicited or spontaneous). Clarify how the sponsor should have oversight for reporting of these events by investigators?

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 796		**Comment:** In section VI.C.2.2.2.2. it is stated that for compassionate and named patient uses where adverse events are actively sought, only reports of adverse reactions where a possible causal relationship with the suspected medicinal product is considered by the primary source *or the marketing authorization holder* should be reported (as solicited reports), whereas in line 791 reference is made to 'an organization (footnote 25) or a HC professional' rather than to only the MAH. **Proposed change (if any):** Line 794-796 should be amended for consistency: 'For compassionate and named patient uses where adverse events are actively sought, only reports of adverse reactions where a possible causal relationship with the suspected medicinal product is considered by the primary source or the ~~marketing authorisation holder~~ organisation should be reported. They should be considered as solicited reports and reported accordingly.'
Line 798-800		**Comment:** During compassionate /named patient use programs, frequently the MAH will have communications directly with HCPs and patients regarding supply. During these communications patient death may be reported (without an explicit causality being mentioned) without the AE being solicited. Would causality have to be assumed as this is considered to be spontaneous? **Proposed change (if any):** Clarification of above and whether the information referred to in lines 364-368 also applies to reports arising from this sort of interaction.
Lines 921-925		**Comment:** '…events / observations, which may affect the risk-benefit balance of a medicinal product…should be notified…immediately'

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): Define 'immediately'.
Line 949		**Comment:** More guidance is needed in regard to how long a MAH should continue reporting when the marketing authorization is withdrawn or revoked. **Proposed change (if any):** Recommend to provide guidance, e.g. 1 year after last expiration date.
Lines 993-1041		**Comment:** This section does not give timelines for reporting. It is mentioned elsewhere. **Proposed changes (if any):** It would be helpful to explicitly state the timelines in this section or at least provide a link to the timelines stated in another section.
Line 1010		**Comment:** It seems as if non-serious ICSRs that occur outside the EU are not required to be reported, so this should be explicitly stated to remove any doubt. **Proposed changes (if any):** Clarify the above by adding the following statement to the end of this section "Marketing authorisation holders

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')*
		are not required to report non-serious ICSRs that occur outside the EU"
Lines 1010–1018 and 1030-1041		**Comment:** It is not clear whether the requirement to submit non-serious ICSRs include those originating from PASS? **Proposed changes (if any):** Explicit clarification of above.
Lines 1190-1192		**Comment:** The guidance is incomplete and assumes there is always a common active ingredient. UK example: BENADRYL® products contain the following active ingredients: BENADRYL® One A Day Relief & BENADRYL® One A Day & BENADRYL® Allergy Oral Syrup & BENADRYL® for Children Allergy solution - Cetirizine (antihistamine); BENADRYL® Plus - acrivastine (antihistamine) & Pseudoephedrine (decongestant); BENADRYL® Allergy Relief - acrivastine; BENADRYL® Skin Allergy Relief - diphenhydramine (antihistamine), zinc oxide and racemic camphor. If reporter only stated "Benadryl", how would this be treated? Is the report valid if the drug is not identifiable? **Proposed change (if any):** Clearer guidance on identifiable medicinal product is required. US guidance on monographs is that if the active cannot be identified, valid ICSR criteria are not met.
Lines 1242-1243 & 1578		**Comment:** A case narrative needs to confirm that no additional information is available and/or that the reporter is unwilling to provide information. It is not clear whether this is for every case narrative (initial & 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')*
		Proposed change (if any): Clarification of the above.
Lines 1323-1324		**Comment:** It is unclear if when an error is made that changes the medical evaluation of the case, what date of receipt should be used during correction - The date the error was discovered or original date of information? This impacts late case assessment. **Proposed change (if any):** Provide clarity on how to handle situations when an error was made that requires correction and resubmission as the data point would impact the medical evaluation of the case.
Line 1820		**Comment:** In Figure VI.3. the word 'case' refers to 'ICSR' – would use this terminology in the figure. In the concerned description (step 3) it is mentioned 'Is case from EU?', whereas in figure VI.3. the question reads 'Is case from *EEA?*' (This needs to be clarified). **Proposed change (if any):** Replace the word 'case' by 'ICSR' in figure VI.3. Clearly differentiate between EEA and EU for consistency.
Line 1824		**Comment:** Step no 1 states ' if case has been received from NCA do not retransmit to EV', which contradicts with line 1001-1002 which states 'MAH shall report to EV all serious ICSRs….including those received from competent authorities'….if appropriate clarify EU NCA cases should be disregarded. **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')*
		Clarify the correct interpretation.
Line 1837		**Comment:** For comments on Fig VI.4, please see comments to Figure VI.3 as mentioned above (i.e. 'ICSR' instead of 'case', clarification on EU vs. EEA).

Please add more rows if needed.

16-Apr-2012

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

Comments from:

Name of organisation or individual
Lambda Therapeutics Limited

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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	For recording ICSRs in MAH's database is MAH expected to select ICSRs which originate from country where they do not have marketing authorization? Example: Literature report originates from Japan/Belgium and MAH don't have any authorization in that country.

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 944		Comment: After drug withdrawal from market till what time MAH is expected to report ICSRs? Proposed change (if any):
Line 999		Comment: During Interim period if report is received from any CMS country (for DCP-MRP procedure) then is MAH expected to report cases to RMS country? Proposed change (if any):
Line 1001		Comment: Is MAH expected to report both expected and unexpected serious reports if it is originated from outside EU. Proposed change (if any):
Line 311		Comment: 1) Is it mandatory for MAH to have its own internet or digital media? 2) At what frequency MAH is expected to screen reports from internet or digital media? Example: like for literature MAH is expected to monitor at least once a week. Proposed change (if any):
Line 328		Comment: In this situation can MAH consider report to be valid? 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')*
Line 843		Comment: Is MAH expected to database such reports? Or can consider under 'Article of Interest' Proposed change (if any):
Line 384		Comment: In this situation should report be considered 'Medically confirmed'? Proposed change (if any):
Line 1442		Comment: Is MAH expected to report Non-serious ICSRs with lack of therapeutic efficacy originating from Non-EU country? Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Friday 13 April 2012

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

Comments from:

Name of organisation or individual
Netherlands Pharmacovigilance Centre Lareb Goudsbloemvallei 7 5237RE 's-Hertogenbosch The Netherlands

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*).*

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1. General comments

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

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 198-202		Comment: Several primary sources, such as healthcare professionals and/or a patient or consumer, may provide information on the same case. In this situation, all the primary sources' details should be included in the case report, with the "Primary source(s)" section repeated as necessary in line with the ICH-E2B(R2) guideline[2] Proposed change (if any):
VI.B.1.2. Solicited reports. Line 340		Comment: "For the purpose of safety reporting, solicited reports should be classified as study reports, and should have an appropriate causality assessment, to consider whether they meet the criteria for expedited reporting" This would imply that any reports in the framework of Intensive Monitoring studies conducted by Competent authorities should be assessed on a continuous basis. This would seriously hamper processing of large numbers of reports and thereby the feasibility to include large number of patients. Proposed change: causality assessment is only required in the event a serious condition has been reported and the case should be forwarded within 15 days.
VI.B.2 line 376		Comment: "Reports for which the minimum information is incomplete should nevertheless be recorded within the pharmacovigilance system for use in on-going safety evaluation activities." This doesn't seem logical if the minimum requirements are not fulfilled. Proposed change: These lines should be skipped
Line 407		Comment: Serious reports should be followed up appropriately to ensure comprehensive case information is obtained, including information on the outcome/resolution of the suspected adverse reaction.

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')*
		However, in the event it is clear from a clinical point of view that additional information cannot be expected, there is no use for additional follow up. Proposed change: This only applies for situations where the outcome is unknown or information is needed from a clinical point of view.
Line 431		Comment: "if the information is incomplete, attempts should be made to obtain consent to contact a nominated healthcare professional to obtain further follow-up information." In many cases assessors(in many cases physicians themselves) may very well ask for clarification by the patient. There is no need to contact the treating physician at all times, especially since he/she is not always able to provide any additional information due to unawareness of the event (e.g. when the consumer reports a rather subjective complaint for which the physician is not contacted such as headache or nausea).
Line 441		Comment: "The reports received from the primary source should be treated in an unbiased and unfiltered way and inferences as well as imputations should be avoided" In the event it is clear that the reported diagnosis is incorrect (for instance in the event op consumer reports), an alternative diagnosis should be made by the assessor. Of course it is possible to mention a diagnosis as 'sender's diagnosis', but signal detection is carried out on the level of the reported diagnosis by the primary source. Interpretation by a qualified assessor is in many cases more valuable than using low quality initial reports Proposed change: Make a distinction between consumer and other reports. Coding that is amended should be documented. A distinction may be made between the obligations for Marketing Authorisation Holders and 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')*
Line 473		Reports where the embryo or foetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure) should be followed-up Proposed change: There is no need to follow medicinal products when they are intended to use during pregnancy for instance folic acid in low dosage. We would propose a more risk based approach, by defining more clearly which products should be monitored. In addition, the risk for exposure via semen is not realistic and not been proven for the majority of drugs. Systematic monitoring of these situations will hamper the cooperation of healthcare professionals and consumers. Only in the event in which a possible risk of exposure via semen is mentioned in the RMP should be monitored.
Line 476		"should be followed-up in order to collect information on the outcome of the pregnancy and development of the child" The wording "development of the child" is vague. We would propose monitoring the development of the child after birth "as specified in the RMP"
Line 480		when assessing the possibility of foetal exposure ….. Given the fact that exposure will take place in the first trimester, the wording is incorrect and should be 'embryonal exposure' Proposed change: …..embryonal exposure….
Line 482		Every effort should be made to obtain information on any possible medicinal product exposure to an embryo or foetus and to follow-up on the outcome of the pregnancy. There is no need to follow medicinal products when they are intended to use during pregnancy for instance

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')*
		folic acid in low dosage. We would propose a more risk based approach, by defining more clearly which products should be monitored for instance by defining the risk in the RMP or by the establishment of a dedicated list of products that should be monitored.
Line 584		Comment:" Where an initially serious case is downgraded to non-serious, this information should still be reported within 15 days" This situation happens quite often when consumer reports are submitted as "other serious condition". If a downgraded initial reports has not yet been submitted to EMA, there is no use for submission within 15 days. Proposed change (if any): make a distinction between those reports which have already been submitted to EMA and those who are not. Please change the wording into "Where an initially submitted serious case"
Line 686-692		Comment: "The forms shall be made publicly available by means….." It is not sensible to make the use of the EMA form that is to be developed, when a local (national) form is already available as long as the type of information to be submitted is the same. Proposed change (if any):make clear that the EMA form is not mandatory as long as the required information can be completed by national or local forms.
Line 775		Comment: " only reports of adverse reactions suspected to be related to the studied medicinal product by the primary source or the marketing authorisation holder should be reported." Not all non-interventional studies are conducted by the MAH, but also by competent authorities themselves. The obligation to submit every reports with a possible causal relationship within 90 days would seriously hamper the possibility to include large numbers of patients and would make studies outside the MAH setting practically impossible. It should be sufficient to mention the reports in the final study reports. The obligation to submit reports to EMA should be limited to expedited 15-days reporting. See also the comments for VI.B.1.2. Solicited reports. Line 340

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 : Make clear that non-serious reports do not require reporting in an expedited way or within 90 days or add "Adverse reaction reporting is not required from intensive monitoring studies (such as Modified Event Monitoring, Specialist Cohort Monitoring studies and Lareb Intensive Monitoring)"
Line 1047		"It will replace the requirements of Member States participating in the WHO Programme for International Drug Monitoring to directly report to WHO suspected adverse reactions reports occurring in their territory." Forwarding to the WHO can only replace the requirement of Member States participating in this programme once the full E2B compatible information is forwarded. When this is not the case and only a limited amount of information is forwarded to the WHO, this will seriously hamper signal detection on the WHO database. Proposed change : make clear that the same information as received by EMA will also be forwarded to WHO. If this is not the case, the sentence 'will replace requirements' should be adapted.
Line 1232-34		Comment: "If no diagnosis is provided by the primary source, all reported signs and symptoms should be listed and MedDRA coded in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'. If these signs and symptoms are typically part of a diagnosis, the diagnosis can be MedDRA coded in addition in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'." This rule will seriously hamper an efficient signal detection in the event an assessor clearly identifies an incorrect diagnosis for instance in the event of an incorrect diagnosis. Proposed change: incorrect diagnoses should be deleted; but should be clarified in the narrative.

Please add more rows if needed.

Guideline on good pharmacovigilance practices: Module VI

Dear Sirs,

as Italian PV responsible person I've been evaluating the relationship between non interventional studies PV and the standard Post Marketing PV rules.
According to Italian laws in force, non interventional studies PV has to be managed according to PM rules.
This said, I've always considered logic consequence the following 3 points:

1) in the context of an hypothetical prospective study n.123 sponsored by company A (MAH of drugs B, C and D) on drug B, if a company A person (or delegate) gets information about an ADR to drug C or D during monitoring activities of study 123, it's Investigator's AND company A obligation to have the ADR reported to Authorities (as belonging to the context of a non interventional study).

2) in the context of an hypothetical prospective study n.456 sponsored by company A (MAH of drugs B, C and D) on the pathology for which drug B is indicated (but not on drug B specifically), if a company A person (or delegate) gets information about an ADR to drug B, C or D during monitoring activities of study 456, it's Investigator's AND company A obligation to have the ADR reported to Authorities (as belonging to the context of a non interventional study).

3) in the context of an hypothetical retrospective study n.789 sponsored by company A (MAH of drugs B, C and D) on drug B, if a company A person (or delegate) gets information about an ADR to drug B (or C or D) during monitoring activities of study 789, it's Investigator's AND company A obligation to have the ADR reported to Authorities (as belonging to the context of a non interventional study). NOTE in this case the ADR should be clearly stated as such in patient file (e.g. "patient stopped therapy with drug B because of a cardiac arrest caused by drug B"). The same would apply if the study is not focused on drug B but is sponsored by company A.

The concept related to the 3 considerations above is that the MAH, in my interpretation, can be considered informed of an ADR also in the context of monitoring activities, and, once informed of an ADR, should be its duty to check if the case was previously reported to Authorities by Investigator. In case of a not reported ADR, should be MAH/Sponsor responsibility to grant its reporting and, in any case, to record the ADR in company database.

What above discussed seems to be in contrast with lines from 775 to 784 of Module VI.

Many thanks and best regards,

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 April 2012

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

Comments from:

Name of organisation or individual
Medicines Evaluation Board – The Netherlands

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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The guidance in this GVP is not yet in line with the ICH E2B(R3) Implementation Guide that is expected to reach Step 4 in November 2012. For example, line 212-216 provide guidance concerning medical confirmation at case level, whereas in ICH E2B(R3) medical confirmation is captured at event level. Is it intended to update this GVP Module when ICH E2B(R3) will be implemented in the EU?

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')*
160-178		Comment: Of the definitions listed here, 'occupational exposure' is not included in the GVP Annex 1 Definitions Proposed change (if any): Add definition of occupational exposure to GVP Annex 1 (this is actually a comment on the GVP Annex 1, not on GVP Module VI, but consistency should be ensured)
400-411		Comment: Line 400 states that *written* confirmation of details given verbally should be obtained whenever possible. In line 405, it is mentioned that it should be avoided to discourage future spontaneous reporting. Always asking for written confirmation might actually discourage spontaneous reporting. Proposed change (if any): Delete the requirement to ask written confirmation of details given verbally.
584		Comment: A case can be reported by the primary source a serious case, but does not necessarily have to be processed as a serious case according to our definitions (e.g. 'hair loss' is often considered serious from a patient perspective, but is not likely to meet our regulatory definition of serious). The 15-day reporting obligation should not apply to such cases. Proposed change (if any): Line 584 should make clear that 'an initially serious case' refers to a case that has been submitted to NCAs, MAHs as a serious expedited report.
Section VI. C.1 Interface with		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')*
safety reporting for clinical trials in the EU		It could be useful to clarify the reporting requirement for the situation where the ADR originates from a clinical trial EEA, when the reaction is suspected to be related only to another authorised medicinal product taken concomitantly, which is not part of the clinical trial protocol, and which does not follow the definition of Non-Investigational Medicinal Product (NIMP). This case should be considered a spontaneous report. Proposed change (if any):
Section VI.C.2.2.4 (also line 1350-1351 in section VI.C.6.2.2.9)		Comment: This section implies that a case narrative should be provided for all cases. However, Annex 1 of the Concept Paper on the Implementing Measures implies that case narratives are only mandatory for serious cases submitted by Marketing Authorisation holders. Proposed change (if any): Please ensure consistency between the final version of the GVP and the Implementing Measures with respect to the case narratives.
Section VI.C.2.2.6		Comment: We consider it very useful that this section clarifies what should NOT be reported as ICSR, but as an 'Emerging Safety Issue'. However, it is not clear how this relates to the MAH obligations described in GVP Module IX Signal Management.
VI.C.6.2.3.2 (literature reports), line 1417-1419		Comment: This section could be interpreted in a way that only upon request a copy of the relevant literature article should be submitted. The concept paper on the Implementing Measures was more strict and implied that a copy should always be submitted and a full translation should be submitted upon request. Proposed change (if any): Please clarify and ensure consistency between GVP and IM
VI. Appendix 1 (Identification of		Comment: Appendix 1 raises some questions how this will work in practice: - Will the checking of batchnumbers for ICSRs containing a biological medicinal product be a manual

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')*
biological medicinal products)		process or will it be automated in EudraVigilance (EV)? - Will it be possible that a Sender receives a positive acknowledgement (01ACK), and still be contacted for follow-up information about the batch-number? Or will a negative ACK (02ACK) be sent if no batchnumber available in the ICSR? In this situation, during the time the Sender is seeking follow-up information about the batchnumber, will the ICSR be available for signal detection and analysis? Although we acknowledge that the batchnumber is very important, a missing batchnumber should not delay the availability of the ICSR for analysis. Or, in the final arrangements (when EMA forwards MAH cases to the MSs), a missing batchnumber should not delay the forwarding to the MSs. - This process will require a list with biological products; can such list be shared with the Member States?
VI.Appendix 5. Nullification of cases, table VI.12		Comment: As consumer cases now qualify for expedited reporting, Line 9 is no longer necessary Proposed change (if any): Delete line 9 in the table

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
MedDRA Maintenance and Support Services Organization (MSSO)

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*).*

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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')*
227 - 232		Comment: The wording of "The IME list is intended for guidance purposes only" may not be sufficiently clear to some organizations submitting ICSRs. Proposed change (if any): For the sake of transparency, the guideline should describe the current and potential **internal** uses of the IME list by the EMA. It should also specifically indicate to the reader that the IME list will not be used as the basis for regulatory compliance monitoring of ICSR reporting by a sponsor.
1218 - 1221		Comment: Between lines 1220 and 1221, the guideline cites that it is sufficient to select a term for only the diagnosis or provisional diagnosis and not for the signs and symptoms. The current MTS:PTC supports selecting a term for the diagnosis only (and not for the signs/symptoms) when the diagnosis is **definitive**. For a provisional diagnosis, the **preferred option** identified in the MTS:PTC is selection of a term for the provisional diagnosis **and** terms for the signs and symptoms. As the guideline currently reads, it is inconsistent with the **preferred option** identified in the MTS:PTC for a reported provisional diagnosis with signs and symptoms. Proposed change (if any): In practice, events, which are typically signs or symptoms of a diagnosis or a provisional diagnosis reported by a primary source, should be listed and MedDRA coded in the section 'Reaction(s)/event(s)' (ICH-E2B(R2) B.2). Selection of MedDRA terms for the diagnosis – definitive or provisional – and terms for signs and symptoms should follow the **preferred options** as identified in the ICH-Endorsed Guide for MedDRA Users, MedDRA Term Selection: Points to Consider.
1445 - 1448		Comment: This section specifies a particular MedDRA term – LLT *Product quality issue* – to be used for a report of a product quality issue. MedDRA contains many Lowest Level Terms (LLTs) describing many forms of product quality issues such as LLT *Product container leak*, LLT *Product closure missing*, etc. Significant specific information could be lost if only the broad LLT *Product quality issue* is used for coding. Note, too, that 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')*
		MedDRA Term Selection: Points to Consider document cites specific LLTs most closely resembling the reported information regarding product quality issues. This guideline should simply refer to the Points to Consider document for selecting the most appropriate and specific LLT for product quality issues. Proposed change (if any): Where an adverse reaction(s) report is associated with a quality defect of a medicinal product, the MedDRA Lowest Level Term for a product quality issue describing most closely the reported information should be selected for the element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1.b. Please reference the latest version of the MedDRA Term Selection: Points to Consider document for advice on selecting a product quality issue term
1450 - 1457		Comment: This section of the guideline calls out two specific MedDRA Lowest Level Terms – LLT *Suspected counterfeit product* or LLT *Pharmaceutical product counterfeit* – to be used when a suspected or confirmed falsified product is recognized. Caution should be advised when citing any specific MedDRA term to be used as MedDRA is constantly changing, and terms may even be made non-current in future versions of the terminology, thus making the guideline out of step with the terminology. Proposed change (if any): Where an adverse reaction(s) report is associated with a suspected or confirmed falsified medicinal product, the MedDRA Lowest Level Term corresponding most closely to the reported information should be added accordingly to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1.b).
1420, 1428, 1446, 1451, 1464		Comment: In several places in the document, there is reference to a MedDRA "Low**er** Level Term". Please note that the correct designation is "Low**est** Level Term". Proposed change (if any): Please change "Lower Level Term" to "Lowest Level Term" in relation to MedDRA terms throughout the document.

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)

Comments from:

Name of organisation or individual
The Monitoring Medicines Consortium

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	According to the proposed EU guidelines on good pharmacovigilance practice, Member States shall have in place a system for collection of reports of adverse reactions from patients and consumers. The guidelines also mention that standard web-based structured forms for the reporting of adverse reactions by patients or consumers shall be developed. **Monitoring Medicines** (MM) is an 11 partner consortium supported by the Framework Programme -7 of the European Commission (grant 223566, www.monitoringmedicines.org). Deliverables of the MM consortium include the development of guidelines and tools for consumer reporting of medicine-related problems. The consortium wishes to bring to the attention of EMA that a guidance document entitled 'Safety Monitoring of Medicinal Products – Reporting system for the general public' was recently published by WHO, a leading partner of the consortium. (www.who.int/medicines/areas/quality_safety/safety_efficacy/EMP_ConsumerReporting_web_v2.pdf). The MM consortium has also worked closely with representatives of several European patient and consumer organizations and competent authorities in developing a web based tool specifically intended for use by patients and consumers for submission of adverse reaction reports. The system provides a generic structure and can be used by any Member State accepting ICSR data in E2b format. Language, style sheets and logos can be adapted to the needs of each Member State. A training workshop was carried out in the Netherlands 7 – 9 March 2012, with representatives of several European regulatory agencies and patient and consumer organizations, providing the first test of the reporting tool. The MM adverse reaction reporting tool for the general public is now ready for use. It is maintained by one of its partners, the Uppsala Monitoring Centre (UMC). Any country wishing to pilot the system is welcome to approach the UMC for further information (info@who-umc.org)

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):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
NORGINE Ltd

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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')*
Line 296-300		Please clarify the statement 'The publication reference(s) should be given as the report source'. What does 'source' mean in the context of this sentence? Is it the report source or reporter source?
Line 556 to 579 *and* *Line 1490 to 1499*		Comment: The clock for expedited reporting of a valid ICSR starts as soon as the information containing the minimum reporting criteria has been brought to the attention of MAH----------. This date should be considered as day zero. Since data element ICH-E2B(R2) A.1.6 should contain the date of receipt of initial ICSR (both valid and non-valid), please confirm whether Day zero corresponds to the data element ICH-E2B(R2) A.1.7 and not A.1.6. Proposed change (if any):
Lines 470 to 536 Lines 1371 to 1490		Comment: VI.B.6 has a heading 'Special Situations', followed by a list of situations. VI.6.2.3 has a heading Special Situations' again followed by a list that does not match VI.B.6. Proposed change (if any): Can the list be harmonised or split into 'Special Situations' for those which match VI.B.6 and create another list with a header 'Other Situations'.

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)

Comments from:

Name of organisation or individual
Norwegian Medicines Agency

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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')*
193		Comment: Is it possible to use another concept than "mutatis mutandis"; it is difficult to translate and understand in our/other languages, and is –as we understand it – a juridical concept which is not easily understood by the relevant readers. Proposed change (if any): ?
206-207 212, 264, 272, 354, 384, 387, 412, 516, 675, 680, 684, 687, 693, 695, 721, 745,		Comment: "Consumer" is defined in lines 206-207 as a person who is not a health care professional such as a patient, lawyer, friend or relative of the patient. In the listed lines both patient and consumer are mentioned as if they were different categories. In light of the definition given, it should be unnecessary to include the word "patient" in these lines. Proposed change (if any): Delete "and patients" from these lines.
215		Comment: "Patient, friend or relative of the patient" is defined as "Consumer" in lines 206-207. The expression consumer should be used throughout the document unless more precise wording is necessary. Proposed change (if any): In line 215 "consumer" should replace "patient, friend or relative of the patient"
222-225		Comment: This is true, except for when persistency (or significant disability) is an important factor in describing characteristics/consequences. Would it be more precise if the sentence is rewritten? Proposed change (if any): Include something on disabling ADRs?
266		Comment: Would it be more correct if it read: regional **pharmacovigilance** centre? Should drug 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')*
		centre and teratology centre be included in the parentheses, as they are mentioned elsewhere? Proposed change (if any): "(e.g. Regional Pharmacovigilance Centre, Poison Control Centre, Drug Information Centre or Teratology Centre)"
293-295		Comment: We find the sentence a bit confusing; what does "This" in the beginning point back at? Proposed change (if any): "Reports identified in the scientific and medical literature that originate in a country where a company holds a marketing authorisation but has never commercialised the medicinal product, should also be considered by the marketing authorisation holder(s)."
(353-356) (374-379) 412-416		Comment: If the reporter is a pharmacist; follow-up of the report can be difficult because the community pharmacies in general (in our country) do not keep a detailed patient journal and might never see the patient again. Reports from pharmacists will often contain details limited by the information the patient has given. These reports will therefore almost always demand requests for additional information. The pharmacies rarely keep the patients contact information and will need the patient's permission to contact their physician (which probably will be necessary to obtain further information). National privacy/confidentiality regulations might therefore limit follow-up. Proposed change (if any): ?
376-378		Comment: "nevertheless be recorded within the pharmacovigilance system" Unclear how reports that does not meet the minimum criteria nevertheless should be included? And where? In our ADR database, it is impossible to register incomplete ICSRs, and we do not understand the purpose of including incomplete ADRs, as essential information is lacking. Are these reports to be registered somewhere else? We do not find in meaningful to include reports lacking essential information (as a drug or an ADR) for signal purposes.

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):
403-406		Comment: Complex sentence makes it hard to grasp the meaning. "The use of targeted specific forms should avoid the requirement to duplicate information already provided in the initial report and/or to complete extensive questionnaires, which could discourage future spontaneous reporting." Proposed change (if any): Rewrite.
407-409		Comment: This is a potentially very resource demanding task, and more guidance on when follow-up can be finalised or considered adequate, would be appreciated (i.e. which outcomes are considered to be "final" etc). Proposed change (if any):
409-411 475-476 472-509		Comment: When embryo or foetus has been exposed to medicinal products; for how long should the report be followed up? Lines 409-411 suggests follow up until the expected date of delivery, but the outcome might not be known at this point. Lines 475-476: Here, follow-up until "information on the outcome of the pregnancy and development of the child" is known is recommended. It is unclear how the time aspect of follow-up of "development of child" should be interpreted; is there a maximum follow-up time regarding the development of the child?
472-509		Gives the impression that all pregnancies where a drug has been taken should be followed-up. Needs clarifying of what and when follow-up is relevant and demanded. Is it all (ADR) reports where a (possible) ADR has been reported early in the pregnancy or all questions/contact from healthcare professionals to the NCAs (or related organisations) regarding exposure of an embryo/foetus to a medicinal product? In our country, the latter would probably demand a new register

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')*
		(which would need to be "authorised" by the government etc). Lines 498-501 implies that all reports of medicinal drug use during pregnancies should be processed as ICSRs also when there is no suspected adverse reaction. These reports, lacking at least one suspected adverse reaction, would not fulfil the criteria for valid ICSRs. Keeping these reports in the same database as valid ICSRs will distort statistics. Proposed change (if any):
533-535 963-970		Comment: It would be useful to include a sentence on whether overdose, abuse, misuse, medication error or occupational exposure, which results in an ADR, are to be considered as serious (Other important medical event, if no other serious criteria is met?). This is also related to the fact that it is a bit unclear for us if non-serious reports are to be considered as expedited (up until now expedited and serious has had (almost?) the same meaning, so some further guidance would be appreciated).
536 536-543 1442-1444		Comment: Reports of lack of efficacy should in certain circumstances be expedited as ICSRs within a 15 days time frame. For instance in cases of use of contraceptives. However, it is also stated that it is acceptable to submit these ICSRs as non-serious. We find this a bit confusing; in our view, treatment of life-threatening diseases and lack of efficacy of contraceptives are by definition serious, and we would regard lack of efficacy of a vaccine (leading to disease) in the same way. In our opinion, cases that are eligible for expedited reporting are also to be coded as serious.

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536-555		Comment: Lack of drug effect may be a result of an unknown (new) drug-drug interaction, counterfeit drugs or quality issues. Reports of lack of drug effect might therefore be important for detecting this type of issues. Proposed change (if any): Could some guidance (for healthcare professionals and patients) on this issue be included in this section?
1159-1217		Comment: It would be useful in this section to include a paragraph on who (the primary reporter, the NCA etc, the MAH) has the final word and decides which drug should be coded as suspect in a report. Are MAHs and/or NCAs permitted to code a drug as suspected, when the primary reporter has reported/evaluated it as concomitant? Are MAHs and/or NCA permitted to make a comment about a disagreement on which drug that should be suspected in the case narrative? The case narrative and the coded suspect drug would in such cases be conflicting.
1236-1251		Comment: Case narrative: We are aware of the previous discussions and the legal obligation on the issue of providing complete case narratives on all serious cases. However, as this is a time consuming task, especially for non-English-speaking countries, we find it important that the case summaries are limited to the information that has not been included (e.g. because it is impossible to code) in the structured fields and information on the sequence/order things happened to the patient. We do not find it possible or worth the time/work to repeat all coded information, especially when the time sequence is possible to read out of the structured data. This is a general comment, but related especially to laboratory test data, medical history and other data such as autopsy data and post-mortem findings. We find it useful to use the case narrative to describe data/time sequence that will **add value** to the structured data. With the limited resources we have, it is important to use our time on tasks that make the reports easier to assess.
1896 table ex 13		Comment: Table VI.12. Example 13. Not nullifying the original case and creating a new will create duplicate reports. Will the duplicate be handled by the EMA, based on A.1.11.2? If not, it would be helpful to know how this duplicate should be handled. Proposed change (if any):

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1914 table no 2		Comment: Table VI.14. No 2. It is unclear which responsible organisation the Duplicate Management Team belongs to. Proposed change (if any): “EMAs Duplicate management team”?

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

March 23rd, 2012

Version date: 11 Jun 2012 17:41

Submission of comments on 'GVP Module VI – Management & Reporting of ADRs (EMA/873138/2011)

Comments from:

EVM
Alcon Inc. Novartis Consumer Health Novartis Pharma AG Novartis Vaccines & Diagnostics Sandoz Pharmaceuticals

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).

Declaration:

The author is signing to confirm that this document has been prepared in accordance with Novartis standards for commenting and impact analyses of regulatory guidelines. The review team has assessed that the operational aspects of this guideline are scientifically appropriate and achievable by the Drug Safety and Pharmacovigilance function. The team has confirmed that the Novartis pharmacovigilance system will be modified appropriately to ensure that the final guidance is met, according to a transition plan to be defined. The Global Head of Pharmacovigilance is signing to confirm sponsorship of process changes and that Novartis will meet the new requirements set-down in the final GVP Modules, subject to approval and to the publication by EMA of a formal transition plan with timelines for Marketing Authorisation holders.

E-signature and date on file: [redacted], Global Head of Pharmacovigilance.

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Novartis is in broad agreement with both the general and detailed comments provided by EFPIA. The guidance within this GVP Module is informative, well-constructed and, in general, pragmatic. Specific points are raised in the text below, including detailed points such as typographical errors. The aim is to ensure that the guideline is robust, complete and of the highest quality.

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')*
158 and 364 to 370		***Comment:*** There is an inconsistency in the reporting requirement for unrelated for spontaneous reports in line 158 versus lines 364 to 370. Line 158 speaks only of "unrelated", i.e. as per ICH definition, whereas line 364 to 370 speaks about excluding a causal relationship. ***Proposed change:*** Line 158: change to state that unless the reporters make an explicit statement that a causal relationship can be excluded as per section VI.B.2.
160 to 178		***Comment and proposed change:*** The definitions in this Module should be identical to those in the Definitions document. ***Additional Comment:*** Definition of 'underdose' is required in the context of vaccines, as this medication error is particularly important in cases of lack of efficacy. In contrast, a lower number of immunisations than recommended does not constitute an underdose (this would be an incorrect vaccination schedule). Since the vaccination volume per single dose may differ from one product to another, this particular detail is a vaccine specific. It must be determined by reference to the SmPC specific for the vaccine product. ***Proposed change:*** Underdose has occurred when less than the recommended volume of vaccine is administered within a single immunisation procedure (as defined in the SmPC).
193 to 196		***Comment:*** The specific and detailed guidance on reporting ADRs from compassionate use and named-patient use is welcomed.
212 to 213		***Comment:*** If a patient cites a laboratory value which is not routinely available does this qualify as HCP-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')*
		Medical documentation or at least evidence of review of medical records should be provided to quality as 'medical confirmation' [line 212 to 213].
229 to 235		***Comment:*** We request that reference to the IME list is removed as a reference point in the context of what constitutes 'serious'. This list was not designed for this purpose and was not approved for this use by the EV EWG (verified from meeting minutes). ***Proposed change:*** Delete from 'The EudraVigilance… [line 229] to MedDRA." [line 235].
253 to 254		***Comment:*** The words 'authentic' and 'verifiable' are used to define attributes of collected case reports. Throughout the rest of the document valid is used. ***Proposed change:*** Make the text and meaning consistent by referring to 'valid' case reports throughout.
284 and 831-832		***Comment:*** The requirement for local literature review is inconsistent between line 284 (all company offices are encouraged to be aware of publications) and 831-832 (journals in those Member states where the medicinal product is authorised). ***Proposed change:*** Add to row 831-832 "Marketing authorisation holder country offices should also…"
298 to 299 & 362 & 843 to 844 1807		***Comment:*** The guidance that gender constitutes an identifiable patient [362] when linked to the requirement to create a case for every identifiable patient in a literature report [298 to 299] suggests that for any gender-specific disease all reports, even in a large scale observational study, would require case reports being created.

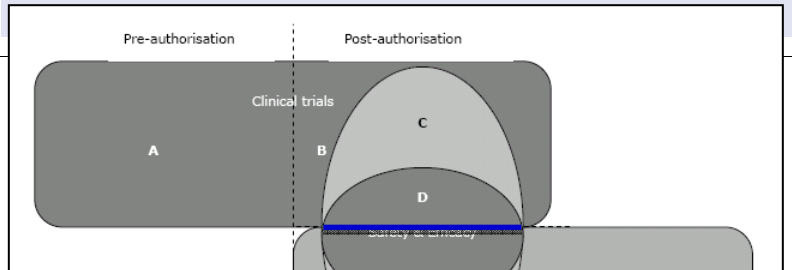
Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Appendix 2 Table VI.2		However, the text in lines 843-844 clarifies the requirement more precisely. It is specified [lines 850 to 855] that safety findings presented in summary analyses should be assessed and any that could affect the benefit risk assessment must be included in the relevant PSUR. Further to this in Appendix 2, Table VI.2 [line 1807] it is proposed to limit ICSRs to three per publication where multiple ICSRs have been reported and patients are identifiable (e.g. by gender only). This is inconsistent with the guidance given within the main text. ***Proposed change:*** Cross-refer 298/299 to 362 and 843/844 and 1807 to provide clear guidance so that only uniquely identifiable patients cited in literature reports require the creation of ICSRs. All uniquely identifiable patients (e.g. age and gender, unique identifying number with age, etc.) should have an ICSR created. In contrast, where a patient cohort is presented in summary analyses and this could affect the benefit risk assessment the evaluation and conclusions drawn from the data should be presented in the relevant Periodic Safety Update Report, not in a series of ICSRs.
310-332		310 – VI.B.1.1.4.Information on suspected adverse reactions from the internet or digital media: ***Comment:*** We broadly agree with the requirements for company sponsored sites, recognising that these may evolve over time. We do not think non-company sponsored sites, including those recommended to be actively monitored in lines 317-320 should be monitored using conventional adverse event collection, see General Comments for further details. **Proposed changes:** Delete lines 317-320: ~~*It is also recommended that the marketing authorisation holder actively monitor special internet sites or digital*~~

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')*
		~~*media such as those of patients' support or special diseases groups in order to check if they describe significant safety issues which may necessitate reporting in accordance with the recommendations described in VI.C.2.2.6. The frequency of the monitoring of those sites or digital media should depend on the risks associated to the medicinal product.*~~ Replace lines 317-320 with: *The MAH is not expected to routinely screen external (non-company sponsored) websites for information on adverse events. If external websites are screened (for whatever purpose), company involvement should be transparent (if possible) and an appropriate process must be in place for the handling of any safety data generated. Appropriate methodology should be used for each activity, with the rationale documented appropriately; this document should be made available to the Competent Authority on request. The methodology can range from collection and analysis of every adverse event to a brief summary in a PSUR as appropriate.* Line 322: *Unsolicited cases of suspected adverse reactions from* ~~*the*~~ ***company sponsored*** *internet or digital media should be handled as spontaneous reports.* Line 325: *In relation to cases from* ~~*the*~~ ***company sponsored*** *internet or digital media…* Delete lines 330-332: ~~*If a marketing authorisation holder becomes aware of a report of suspected adverse reaction described in a non-company sponsored digital media, the report should be assessed to determine whether it qualifies for expedited reporting.*~~
327		***Comment:*** Reports from valid email address are to be considered valid. This is not always appropriate, as there have

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')*
		been instances of fraudulent or malicious reporting. ***Proposed change:*** The recipient should make reasonable attempts to verify the authenticity of reports received via email.
384 to 390 & 1888, Table VI.11, Row 5		***Comment:*** Guidance in 384 to 390 is inconsistent with the ICH E2B (R2) guidance on case nullification [c.f. Table VI.11, line 1888, row 5]. Within section VI.B.2 MAHs are instructed to code and submit a medically-refuted report (e.g. if a patient claims to have "anaemia" but lab data and the opinion provided by a haematologist do not support this diagnosis). However the ICH E2B (R2) document supports case nullification if *"…it is confirmed that the reported adverse reaction(s) did not occur in the patient."* ***Proposed change:*** Cross-refer VI.B.2 to the nullification rules in Table VI.11. Clarify that if the attending HCP provides evidence to refute the occurrence of an ADR reported by the patient then the MAH should submit a nullification report [in accordance with ICH E2B (R2) line 1888, Table VI.11, Row 5].
406		***Comment*** The request for confirmation in writing will not be workable in practice because it will be overly burdensome for MAH and HCPs, even if pre-populated forms are used to reduce burden. ***Proposal:*** Delete the following text from line 400: ~~*Written confirmation of details given verbally should be obtained whenever possible.*~~
400 to 411 & 747 to 749		***Comment:*** No provision is made within 400 to 411 [***VI.B.3***] for electronic source data. ***Proposed change:*** Text should be added in recognition of the use of electronic methods for reporting of safety data. A cross-reference should be made to lines 747 to 749 where electronic reporting is recognised and encouraged.
432 to 434		***Comment:*** The guidance requires further clarification or specification of the limits of the proposed reconciliation processes which should be undertaken. Confirmation of receipt may be sufficient in which circumstances, for example? Where MAHs receive ICSRs directly from NCAs is a confirmation or reconciliation process required?

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')*
450		***Comment:*** The requirement to regularly review databases to identify duplicates ICSRs will be disproportionately burdensome. It should be sufficient to perform the duplicate check at data entry stage, potentially also to perform a duplicate check during generation of aggregated reports. **Proposed change:** Delete line 450: ~~*Databases should be reviewed regularly to identify and manage duplicates ICSR.*~~ And replace with: *A procedure shall be in place to account for identification and management of duplicate cases on a regular basis.*
465 - 469		***Comment:*** Line 465 to 469 states *"Staff directly performing pharmacovigilance activities, and other personnel working in other departments who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be appropriately trained in applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake".* ***Proposal:*** We feel that training on "adverse event collection and reporting" is sufficient for other personnel working in other departments rather than training on applicable pharmacovigilance legislation and guidelines. Pharmacovigilance legislation and guidelines are extremely broad in scope and mostly not applicable to their role with the exception of AE collection and reporting. We propose training is therefore limited to this activity. ***Proposed change to lines 465 to 469:*** *Staff directly performing pharmacovigilance activities, ~~and other personnel working in other departments who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control)~~ should be appropriately trained in applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake.* ***Personnel***

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')*
		working in other departments who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be appropriately trained in adverse event collection and reporting in accordance with internal policies and procedures.
514		***Comment:*** The phrase "Every attempt…" is too strong in this scenario. ***Proposed change to line 514:*** ~~*Every attempt*~~ ***Reasonable attempts****…*
537		***Comment:*** Please provide a definition of lack of efficacy in GVP Annex 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')*
568		***Comment:*** There is no definition of Day 0 when the MAH is screening external databases (such as the FDA AERS or VAERS outputs which include ICSRs). ***Proposal:*** For all ICSRs retrieved from external *[non-MAH owned or sponsored]* databases (such as AERS and VAERS) the clock starts with the day of awareness i.e. on the first business day that the data were received.
550 to 555		***Comment:*** Specific requirements are provided concerning the processing and reporting of lack of efficacy with vaccines. It is important to clarify that this does not extend to biologicals. ***Proposed change:*** Add text to stipulate that the special reporting requirements for lack of therapeutic efficacy with vaccines do not extend to biologicals.
597 to 598 & 603 to 605		***Comment:*** If lines 597 & 598 apply then lines 603 to 605 are unnecessary (and vice versa). ***Proposed change:*** Delete lines 597 to 598 and all subsequent references to the use of the current ICH guideline. The text in 603 to 695 is clear and comprehensive. All subsequent references to the use of the currently applicable Ich guidelines should then be cross-referred to this statement. Alternatively the text could be included in the preface, or in an appropriately placed and cross-referenced footnote to the existing introductory text.
653 Figure VI.1		***Comment:*** Figure VI.1 is incorrect. There is no differentiation between post-authorisation clinical trials and non-interventional studies. ***Proposed change:*** A solid line must be drawn between D and E as shown, in order to differentiate interventional clinical trials from non-interventional studies. 

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')*
708		***Comment:*** In order to ensure timely availability of adverse event information in EudraVigilance, it is important that the phrase 'in a timely manner' (line 708) is replaced with an explicit timeline consistent with the timelines for marketing authorisation holders. ***Proposed change to line 708:*** *… ~~in a timely manner~~* ***within 15 or 90 days for serious and non-serious reports respectively.***
750		***Comment:*** 750 – VI.2.2.2. Solicited reports This section states that solicited reports arise from organised data collection schemes and lists what these activities could be. Some of these activities can generate reports that should be treated as spontaneous reports (see line 801 – Patient support programmes). ***Proposed change:*** Suggest the following edit to avoid readers misunderstanding this point: Line 753: *In the context of this module, these solicited reports are ~~those~~* ***often*** *derived from organised data collection schemes initiated, managed, or financed by marketing authorisation holders and that do not fall under the scope of the clinical trials Directive 2001/20/EC.…*

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')*
767		***Comment:*** The timeframe for collection of all suspected ADRs, including non-serious, within the safety database is both significant and important to industry. Previously non-serious suspected ADRs have routinely been managed on the applicable clinical database. It represents a significant change to business processes to have to manage all of these ICSRs on the global safety database. ***Proposed action:*** We request that this guidance is applicable only to programmes which are approved and commence after ***July 2013***. There should be no requirement for MAHs to populate non-serious ADRs in the form of backlog legacy data from completed and ongoing studies into the global safety database.
801-818		801- VI.C.2.2.2.3. Patient support programme ***Comment:*** Lines 267-268 (VI.B.1.1.1. Spontaneous reports) states: *A spontaneous report …does not derive from a study or any organised data collection schemes as defined in VI.B.1.2.* A similar statement is made in lines 334-336 regarding solicited reports. The above statements are contradicted in lines 813-816 which state the following: *For organised data collection schemes where adverse event reporting is not solicited, any noxious or unintended response to a medicinal product which is notified to the marketing authorisation holder by a patient or healthcare professional should be considered as a spontaneous report of suspected adverse reaction and reported accordingly.* There is an apparent contradiction between the two sections which may lead to non-compliance. ***Proposal:***

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 lines 267-268 can not be changed (because they are in ICH E2D), we propose that lines 813-816 are amended as shown below to minimise confusion. ***It is recognised that according to the definition of a spontaneous report in ICH E2D that these cannot originate from an organised data collection scheme. However*** ~~*For*~~ *organised data collection schemes where adverse event reporting is not solicited, any noxious or unintended response to a medicinal product which is notified to the marketing authorisation holder by a patient or healthcare professional should be considered as a spontaneous report of suspected adverse reaction and reported accordingly.*
750-818		***Comment:*** Lines 750-818 under section VI.C.2.2.2. Solicited reports: We propose to add a similar section on market research programmes as there is now for compassionate use and Patient support programmes. Market research is not per se a patient support programme, but can be an organised data collection scheme. Therefore, it would be welcome to get some more detailed guidance on handling these types of reports. **Proposal: add a section VI.C.2.2.2.4 Market Research** 'Market research programmes are defined as the systematic design, collection, analysis and reporting of data and findings, relevant to Marketing and Business Development decision making.' Similarly to Patient Support Programmes, adverse event reports may be solicited or considered as a spontaneous report of suspected adverse reaction and reported accordingly. For market research services, or surveys where data are collected independently of an individual company and available to purchase to a number of Pharmaceutical companies who have not influenced the original design (including programmes referred to as Syndicated Patient Level Diary studies) there is no obligation on the supplier to report adverse events contained within the diaries to MAHs.'
843 to 844		***Comment and proposed change:***

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')*
		Cross-refer to line 362 as this statement clarifies the requirement.
850		***Comment:*** Line 850 - currently states "The safety findings presented in these types of articles should however be discussed in the relevant sections of the concerned periodic safety update report"... which is inconsistent with the PSUR section on Literature. The latter states that " This PSUR section should include a summary of new and significant safety findings, either published in the peer reviewed scientific literature or made available as unpublished manuscripts, when relevant to the medicinal product, that the MAH became aware during the reporting period"...so the elements of " new and significant" and " awareness " are missing in this module. ***Proposed change:*** The **new and significant** safety findings presented in these types of articles **which have become available to the MAH** should however be discussed in the relevant sections of the concerned periodic safety update report.
921-928 **&** **1154**		**Line 916: VI.C.2.2.6 Emerging safety issues** ***Comment:*** The word 'forthwith' in the Directive is ill-defined. The module makes clear that these notifications should occur only if the events/ observations affect the benefit: risk balance of a product, but then requires that this notification be done '*immediately when becoming aware of them*'. Reiterates the above requirement as it states *'immediately notified'* ***Proposal:*** Replace text and add to line 1154 '*immediately* ~~*when becoming aware of them,*~~ ***and no later than within 15 calendar days, if this affects the benefit risk balance of the product***'.
961		Line 961 – VI.C.2.2.10. Reports from class action lawsuits ***Comment:*** EFPIA welcome the inclusion in the guidance of an exemption to ICSR reporting in extenuating circumstances. ***Proposed change:*** We agree with the proposed exemptions for serious reports. In addition, we request an exemption for follow-

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		up reports of up to 60 days for a company that has received a large batch of legal cases, consistent with the situation in the US.
1017-1018		***Comment:*** We appreciate the inclusion of an Appendix to summarize the member state requirements for reporting of serious non-EU ICSRs and non-serious EU ICSRs in the final Module. We propose to include a requirement to maintain this Appendix updated through the EMA website. ***Proposal:*** Insert after line 1018: *To ensure compliance, Appendix 3.1 will be maintained as a living document on the EMA website throughout the duration of the transitional period*
1135 to 1136		***Comment:*** Reference not necessary, already covered in 603 to 605 (assuming 597 to 598 is to be deleted). ***Proposed change:*** Cross-refer to the statement in 603 to 605.
1396		***Comment:*** The reference to early spontaneous abortion e.g. first trimester should be defined with a timeframe. ***Proposed change:*** Early spontaneous abortion may occur up to the point at which the fetus becomes viable, usually around the 20th week after conception.
1527 to 1529		***Comment:*** Please clarify the frequency of feedback from the proposed quality reviews, as this will aid planning.
1779 to 1783		***Comment:*** Consideration of copyright may that mean the sharing of PDF versions of literature articles is not allowed. The MAH should only provide the literature reference on these occasions. ***Proposed change*** (line 1779), insert bold 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')*
		Literature articles reportable to the Agency should be provided in PDF format ***(taking into account copyright considerations)*** *and sent via e-mail* Insertion in line 1783-1786: *marketing authorisation holders are recommended to consider potential copyright issues specifically as regards the electronic transmission and handling of electronic copies in the frame of regulatory activities.* ***When submission of a PDF is not allowed for reason of copyright, a literature reference will be acceptable.***

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')*
1888, Table VI.11, Row 5 & 384 to 390		***Comment:*** See earlier comment and request for consistency and an appropriate cross-reference between the specified requirements.
Editorial 269 311 331 334 384 435 450 457 489 578 590		**Typographical errors** occur => occur**s** internet => Internet **sites** [or domains] media => **medium** in ICH-E2D => in **the** ICH-E2D of suspected => of **a** suspected anonymous format => anonym**ised** format duplicates => duplicate**d** permit for the => permit ~~**for**~~ the structure => structure**d** cases => case~~**s**~~ reactions => reaction~~**s**~~

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')*
609		EU specific => EU-specific
760		cases => case~~s~~
782		reactions => reaction~~s~~
1318		Omit 'the' [2nd word]
1527		ICSRs => ICSR~~s~~
1810		cross referenced => cross-referenced
1812		cross refer => cross-refer
1854		icsrs => **ICSRs**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
Novo Nordisk A/S

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Comment regarding the concept of spontaneous safety reports Novo Nordisk appreciates the need to refer to ICH for definitions and the efforts to make clear what is meant by an "unsolicited communication that describes one or more suspected adverse reaction". We also appreciate the clear intention to ensure that not any adverse event occurring in connection with the use product pr. default are being recorded as a suspected adverse reaction (only those that are being reported). In addition, according to normal practice, if a patient or health care professional incidentally mention an adverse event during an unrelated contact with a company representative, the representative may suspect a causal relationship, and therefore record the information as a suspected adverse reactions. This is often the case for incidentally mentioned symptoms or diagnoses mentioned in the adverse reactions section of the approved product label. However, the knowledge of the label vary considerably depending on the primary task of the employee, a company representative working for sales and marketing of the product in question may know the label by heart, whereas an employee from production may not even know the names of all products launched by the company he or she is working for. We would like the requirements further clarified, see specific proposal for line 275 below. **Term Expedited reporting** It is confusing that the term Expedited reporting refers to both 15 and 90 day reporting. Normally, the term expedited reporting refers to 15 days reporting. Please, use the term Expedited for 15 days reporting only and use e.g. "Individual Case Safety Reporting" when referring to submission of 15 as well as 90 day reporting. **Comment regarding screening of non-company sponsored web pages** We appreciate the request to actively monitor selected internet sites for "significant safety issues" as opposed to "any suspected adverse reactions".

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')*
275		Comment: For clarity and consistency. Proposed change (if any): Add text (after line 275): "All employees of the marketing authorisation holder must record any suspected adverse reaction, which are being intentionally reported to them as representatives of the marketing authorisation holder."
317		Current GVP draft text: "It is also recommended that the marketing authorisation holder actively monitor special internet sites or digital media such as those of patients' support or special diseases groups in order to check if they describe significant safety issues…" We fear that the word "recommendation" will be interpreted by some inspectors as a requirement, even if the company based on a risk assessment have evaluated that such monitoring is highly unlikely to reveal new "significant safety issue" e.g. old well-known substances or other low risk products. Proposed change (if any): Replace text with: The marketing authorisation holder should consider the possible value of actively monitoring special internet sites or digital media such as those of patients' support or special diseases groups in order to check if they describe significant safety issues…". The rational should be documented in writing.
330 - 332		Current GVP draft text: "If a marketing authorisation holder becomes aware of a report of suspected adverse reaction described in a non-company sponsored digital media, the report should be assessed to determine whether it qualifies for expedited reporting."

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: Please, clarify that the requirement to record all suspected adverse drug reactions (as opposed to significant safety issues) does not refer to internet sites already being actively monitored for significant safety issues. Proposed change (if any): Replace text with: If a marketing authorisation holder becomes aware of a report of suspected adverse reaction described in a non-company sponsored digital media that are not being actively monitored for significant safety issues, the report should be assessed to determine whether it qualifies for expedited reporting.
473-475		Current GVP draft text: "Reports where the embryo or foetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure) should be followed-up in order to collect information on the outcome of the pregnancy and development of the child." Comment: With the current wording, following up on pregnancies may be regarded as a requirement in any case, where the partner is using a medicinal product. However, this should not be a requirement for drugs which are neither genotoxic nor excreted via semen. Proposed change (if any) Please rephrase to: "Reports where the embryo or foetus may have been exposed to medicinal products (either through maternal

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')*
		exposure or transmission of a medicinal product via semen following paternal exposure) should be followed-up in order to collect information on the outcome of the pregnancy and development of the child. In cases where the male was using the product, this requirement does not apply for drugs which are not genotoxic and not excreted via semen.

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
Procter & Gamble

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1. General comments

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

2. Specific comments on text – P&G

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 5 line 158 and page 12 line 366		Comment: Page 5 line 158 – this refers to events being unrelated to the medicinal product while on page 12 line 366 it refers to events being excluded – is this consistent? Proposed change (if any): Ensure consistency
Page 6 line 189		Comment: Use of "Since" is confusing at the start of the sentence Proposed change (if any): or trade names of the medicinal product. A medicinal product is authorised with a defined
Page 10 line 293		Comment: "This also applies.." use of these words is confusing Proposed change (if any): Reword
Page 22 line 740		Comment: could you clarify the word "concluded in this sentence? Proposed change (if any)
Page 25 paragraph starting at 843		Comment: does this mean if there is a literature report with a table that contains enough detail to qualify as a valid report, if it is serious it does not need reporting within 15 days? Proposed change (if any)
Page 25 line 845		Comment: surplus "s" after "article" Proposed change (if any): literature article describes adverse reactions, which occur in a group of patients with

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')*
		a designated
Page 26 section C.2.25		Comment: why has the transmission of an infectious agent been removed from the definition of serious but requires 15 day reporting? Proposed change (if any): clarification of the change
Page 40 – section 6.2.3.5		Comment: Why are the EMA dictating the LLTs that should be used for quality defects or falsified medicinal products Proposed change (if any): Allow MAHs to determine the most appropriate coding

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
Pfizer

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall, this draft module (GVP Module VI – Management and reporting of adverse reactions to medicinal products) is very comprehensive and provides detailed and helpful guidance on the collection, data management, and reporting of suspected adverse reactions associated with medicinal products authorised for human use in the EU. We applaud the Agency for efforts to provide comprehensive guidance. Further, we appreciate the opportunity to review this document and provide the following comments with the goal of improving, and thereby strengthening, the final guidance.
	We reference the extensive comments made by the European Federation of Pharmaceutical Industry Associations (EFPIA), which we fully endorse, and we also offer the following additional suggestions to improve the Guideline. We would be glad to meet with representatives of the Agency to provide clarification on our comments.
	In addition to the comments provided by EFPIA, we have the following general concerns: (a) **Case validity**. The distinction between a valid case, e.g., for PSURs, and a valid case for expedited reporting is blurred (e.g., line 501). Section VI.A.2 and GVP Annex I should contain specific definitions for these important terms. (b) **Identifiable reporter**. For expedited reporting, the focus is on contact details. If the patient would like to remain anonymous and contact details are not available (or only partially available), it seems that an otherwise valid ICSR should qualify for expedited reporting, but would not using the criteria on lines 355-356: "*For the reporter to be considered identifiable, contact details need to be available in order to confirm or follow-up the case if necessary*." (c) **Incomplete consumer information**. It appears that medical confirmation is required to complete an initially incomplete consumer report or to obtain acceptable follow-up information, per lines 413-416: "*When information is received directly from a patient or consumer suggesting that an adverse reaction may have occurred, if the information is incomplete, attempts should be made to obtain consent to contact a nominated healthcare professional to obtain further follow-up information.*" Note that the CIOMS V report indicates that a non-serious

Stakeholder number *(To be completed by the Agency)*	General comment
	labelled/listed case reported by a consumer is considered ‘complete’ when the four elements are available.

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')*
1346-1359		**Comment:** After transition to the new ICSR reporting scheme, when the MAH will submit ICSRs directly to EudraVigilance and not to NCAs, the MAH will not need to provide ICSRs to EudraVigilance that are customised to an individual Member State's separate requirements. **Proposed change**: Add the following new paragraph after line 1359: "***After transition to the new ICSR reporting scheme, when the MAH will submit ICSRs directly to EudraVigilance and not to NCAs, the MAH will not need to provide ICSRs to EudraVigilance that are customised to an individual Member State's separate requirements***.'

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2012

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

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	PHARMIG, the association of the Austrian pharmaceutical industry, would like to thank for the opportunity to comment on GVP Module VI – Management and reporting of adverse reactions to medicinal products.
	In general we want to point out that the overall timeframe of the consultation was very short for an in-depth analysis and commenting on this comprehensive guidance documentation.

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')*
278		Comment: risk-benefit balance Proposed change (if any): Please change to "Benefit-risk balance" and use this term throughout the whole document.
293 - 295		Comment: This also applies to reports identified in the scientific and medical literature that originate in a country where a company holds a marketing authorisation but has never commercialised the medicinal product. Proposed change (if any): Please explain the background and the correlation to lines 291 to 293. Please give examples.
338 – 339		Comment: Adverse reactions reports obtained from any of these data collection systems should not be considered spontaneous. Proposed change (if any): This is not in accordance with the paragraph from line 767 "VI.C.2.2.2.1. Reports from non-interventional studies"
1896		Comment: Please clarify the difference between examples 8 and 13. Proposed change (if any):

Please add more rows if needed.

<17 March 2012>

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

Comments from: Pierre Fabre Group

Name of organisation or individual
Pierre Fabre Group

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Pierre Fabre recognizes the importance to monitor company sponsored websites. Pierre Fabre however has concerns regarding the new proposal to routinely monitor digital media sources which are not company sponsored. The current proposals would constitute a significant burden for pharmacovigilance departments and is likely to increase the number of no added value case reports . Moreover, it does not appear consistent with the risk proportionality principles and is unlikely to result in improved public health protection.

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 160-178		Comment and proposed change: The definition in this section should be the same as those in the Definitions document
Lines 166-169		Comment : Should we understand that an intentional prescription by a physician in a non authorised indication is not an off-label use and should not be dataentered and considered and discussed as a misuse? Even if the safety officer of the company knows this practice is inappropriate because at risk ? It is to be mentionned that the term "inappropriate" in the definition also leaves place to interpretation.
Lines 189-192		Comment : Is this applicable for the MAH partner' s product (marketed in US in cream form for ex) if the EU MAH markets the same active substance but in gel form and in a different indication. Should the EU MAH report its partner cases to EMA ? Propsed change : It is suggested that this situation be clarified for an appropriate reporting for this type of situation
Lines 208-209		Comment : It is mentionned : "*Medical documentations …that support the occurrence of the adverse drug reaction,* ***or*** *which indicate that an identifiable health care professional suspects a causal relationship…are sufficient to consider the spontaneous report as confirmed by a health care professional"* The medical documentation does not imply that a HCP suspected a causal relationship. It is a medically confirmed event (AE) but not necessarily a HCP suspected adverse drug reaction (ADR) Proposed change:

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')*
		Change in the above sentence "***or***" by "***and***"
Lines 293-294		Comment and proposal For seak of clarity , could it be added that *"a literature case originated from a country where a MAH has no MA is not to be dataentered"*
Lines 310-332		Comment: Information on suspected adverse reactions from the internet or digital media: We agree with the requirements for company sponsored sites We do not think non-company sponsored sites, including those recommended to be actively monitored in lines 317-320 should be monitored routinely Proposed changes: Delete lines 317-320: ~~*"It is also recommended that the marketing authorisation holder actively monitor special internet sites or digital media such as those of patients' support or special diseases groups in order to check if they describe significant safety issues which may necessitate reporting in accordance with the recommendations described in VI.C.2.2.6. The frequency of the monitoring of those sites or digital media should depend on the risks associated to the medicinal product."*~~ Line 322: *"Unsolicited cases of suspected adverse reactions from ~~the~~* ***company sponsored*** *internet or digital media should be handled as spontaneous reports."* Line 325: *"In relation to cases from ~~the~~* ***company sponsored*** *internet or digital media…"*
Line 450		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 requirement to regularly review databases to identify duplicates ICSRs will be repeatedly burdensome. It is deemed sufficient to perform the duplicate check at data entry stage, knowing that duplicate reports may also be identifed during generation of aggregated reports. Proposed change: Delete line 450: ~~*Databases should be reviewed regularly to identify and manage duplicates ICSR.*~~ And replace with: *"A procedure shall be in place for identification and management of duplicate cases on data entry cases and on additional time points (for ex during generation and analysis of aggregate reports)"*
Lines 465 - 469		Comment : Line 465 to 469 states *"Staff directly performing pharmacovigilance activities, and other personnel working in other departments who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be appropriately trained in applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake".* Mandatory training process on "adverse event collection and reporting" is deemed sufficient for other personnel working in other departments , all the more that pharmacovigilance legislation and guidelines are broad in scope. Proposed change : *"**A documented appropriate process to specifically train** staff directly performing pharmacovigilance activities, and other personnel working in other departments who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) **on report identification and processing activities** ~~should be appropriately trained~~ in ~~applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake~~ **should be in place**. **Moreover personnel working in non pharmacovigilance departments (e.g. clinical development, sales, medical information, legal, quality control) may in addition 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')*
		trained in applicable pharmacovigilance legislation and guidelines relevant to their work with pharmacovigilance department
Line 514		Comment : The phrase "Every attempt…" seems too strong . Proposed change : ~~*Every attempt*~~ ***Reasonable attempts****…*
Lines 527-528		Comment : It is not clear if this should mean that reports of abuse, misuse, …without associated reaction are not to be considered as non serious ICSRs to be transmitted in 90 days ? In this case , it would raise a concern regarding the quick identification by signal detection in Eudravigilance of potentially important abuse or misuse that may even be surveyed as important potential risks in risk management systems , even if not all of these cases have been associated with an ADR. Proposed change : " *Reports of overdose, abuse , …with no associated adverse reaction should not be reported in an expedited manner as serious ICSRs* ***but should be dataentered and submitted as non serious ICSRs within 90 days*** *. Moreover they should be …"*
Lines 627-629		Comment : It sometimes happens that a serious ADR occuring with a marketed product being an IMP or a non IMP during a clinical trial sponsored by another company is made available to the MAH of the marketed product. Should the MAH submit this case with its product in Eudravigilance database ? Only if a SUSAR ? Never? The sentence in lines 627 to 629 seems to mean that the only notification to be made is to be made by the sponsor of the clinical trial (in CT database) and not by the MAH of this medicinal product (in Eudravigilance) if this one becomes aware of this SADR. Proposed change : Could a clarification be added ?
Lines 833-838		Comment : A slight inconsistency with line 294-295 leading to possible confusion may be to be considered "*Ownership exclusion based on primary source country or country of origin of the sustpected ADR* ". If 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')*
		MAH has a MA but is not yet marketing the product in this country , the MAH could consider to exclude its ownership . This is in contradiction with what is said in lines 294-295 Proposed change : We suggest addition of a clear sentence regarding necessity to dataentry and submission of literature ICDRs in case of MA with or without marketing in the concerned country
Lines 843-844		Comment : *"Literature articles ,…which only detail patients in tables or line listings, should not be reported as ICSRs"* In some publications, patient , ADR and medicinal product are mentionned and the author could be considered the reporter. As the four elements are present, is it still not require to create a case in the MAH database ? Proposed change : For seek of clarity :*"Literature articles ,…which only detail patients in tables or line listings, should not be reported as ICSRs* ***even if data regarding identifiable patient, suspected ADR and suspected medicinal product are provided in the tables*** *"*
Lines 921-928 and 1154		Comment: The module makes clear that notifications of emerging safety issues should be considered only if the events/ observations affect the benefit: risk balance of a product, but then requires that this notification be done '*immediately when becoming aware of them*'. In the Directive , the word 'forthwith' is ill defined. It is suggested to precise a timing for notification of these situations. Line 1154: the above requirement '*immediately notified*' is repeated Proposed change : Add to lines 924 and 1154 '*immediately when becoming aware of them*~~,~~ ***and no later than within 15 calendar days***
Lines 947-948		Comment : In case a MAH is made aware of a serious ADR after its MA has been withdrawn , is it mandatory for the "ex

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')*
		MAH" to submit the case in EV ? The faisability to submission in compliance to E2B requirement as it won't be linked anymore to an existing MA should be considered ? Moreover the term "encourage" will lead to inhomogeneous decisions by different companies and may be understood in a non consistant manner during inspections
Lines 1017-1018		The inclusion of an Appendix to summarize the member state requirements for reporting of serious non-EU ICSRs and non-serious EU ICSRs in the final Module is welcomed. This Appendix should be maintained updated through the EMA website. Proposed change : Addition after line 1018: *"**Appendix 3.1 will be updated on a on going basis and made available for MAHs on the EMA website throughout the duration of the transitional period"***

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
Pharmaceutical Information and Pharmacovigilance Association (PIPA)

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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')*
Line 142-147		Comment: What is the expectation regarding adoption of the new AE definition given that it is now different (although similar meaning) from the ICH definition accepted and used worldwide - in a global company with standard SOPs there will need to be one standard AE definition used. Proposed change (if any):
Line 189		Comment: Please clarify if for a combination product, ICSRs related to a single active ingredient even if not marketed as a single product by the MAH need to be captured i.e. from the literature Proposed change (if any):
Lines 317-321		Comment: Monitoring special interest sites which are not sponsored by the MAH is a resource intensive activity and the value and quality of the information likely to be found is questionable. If this is a recommendation, how many MAH are truly going to be able to do this ? Also there is the potential again for duplication of effort and communication of signals by different MAHs for the same active ingredient e.g. innovator and generic companies. Proposed change (if any):
Lines 947-949		Comment: What time period is considered acceptable for example to continue searching the literature for such reports

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')*
		(especially if there are still are other MAH for the active ingredient)? Is it expected that this should continue indefinitely or for e.g. for 12 months following withdrawal? Proposed change (if any):
Lines 1011-1013		Comment: Details of which CA will require non-serious ADRs in an expedited manner are needed ahead of July to ensure that processes are adapted to accommodate. Proposed change (if any):

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19.04.2012

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

Comments from:

Name of organisation or individual
la Roche

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Roche supports the comments EFPIA has sent in. The modules are in general well written but would benefit from consistency checks across in terms of definitions and requirements for the quality system. In particular Module I describes that, in each module, particular quality aspects will be discussed, and as this is clearly the case in a number of modules, it is less obvious in other modules. For this module, we have no comments in addition to the EFPIA comments. However, please find one question for clarification in the outcome comlumn. In addition, we want to express our support for the concerns raised around the provisions mentioned in section VI.B.1.1.4. Information on suspected adverse reactions from the internet or digital media; we would recommend that the agency deletes lines 317-321 and enters into a dialogue with industry and patient organisations on how to best deal with this situation before formalising this in this module.

req

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')*
229		IME list is mentioned here, however we do miss a clear recommendation. Will that be included in the final version?

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 Apr 2012

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

Comments from:

Name of organisation or individual
Sandoz International GmbH, Industriestraße 25, D-83607 Holzkirchen / Germany

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
	Information on suspected adverse reactions from non-MAH sponsored Internet or digital media (VI.B.1.1.4): The current proposal would lead to a significant burden on the databases, which might not necessarily be adding a value. This approach is mirrored by many concerns such as risk of duplicate reporting and concerns around quality of the information, feasibility and appropriateness of follow-up. CIOMS V states there is no obligation to report adverse events from secondary care databases as the information does not originate from defined projects and can be generated by multiple individuals for various reasons and uses, which is similar to the current internet or digital media.

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 152-156 Lines 360-364		Comment: 'causality' Inconsistency in the text. In lines 152-156 it is mentioned 'unrelated' and in lines 360-364 it is 'excluded'. Proposed change (if any): 'unless the reporters specifically state that they believe the events to be unrelated or a causal relationship can be excluded.
Lines 280-282		Comment: 'Company offices on literature reports' The current wording states that all company offices are encouraged to be aware of publications. Proposed change: It should be 'the country offices where the product is authorized or Country offices holding the MA should.'
Lines 306-328		Comment: 'Information on suspected adverse reactions from non-MAH sponsored Internet or digital media' This should be applicable for only company sponsored internet or digital media. See General comments above. Proposed change (if any):
Lines 372-374		Comment: 'recording of reports without minimal information' This module states that the reports with incomplete minimal information should nevertheless be recorded in the PV system for use in ongoing safety evaluation activities. However, this is in contradiction to Module IX on Signal Management (Lines 186-189, IX.B.3.2.1)

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):
Lines 461-465		Comment: 'training on pharmacovigilance activities' In the current text, staff performing PV activities and other personnel who may receive or process safety reports are considered in the same light. These two groups should be separated for the training requirements Training on 'PV legislation and guidelines' is not warranted for the other personnel. Proposed change (if any):
Lines 510-513		Comment: 'Age particulars for paediatric or elderly population' Currently stated 'every attempt'. Proposed change (if any): This should be replaced with 'reasonable'.
Lines 844-846		Comment: 'Reports published in scientific and medical literature' Currently stated 'The safety findings presented in these type of articles should be discussed in the PSUR'. Proposed change (if any): This should be replaced with 'New and significant safety findings which the MAH has become aware of '.
Lines 957-958		Comment: 'reporting of large batches of potential ICSRs' In line with the Serious ICSRs, a request for the non-serious ICSRs should also be considered.

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 1775-1778		Comment: 'potential copyright issues to be considered when mailing literature articles' Proposed change (if any): In line with this an option is requested to provide the literature reference in a case of a copy right issue.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17.04.2012

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

Comments from:

Name of organisation or individual
SciencePharma

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Could you please explain the possibility of not providing details of the reporter described in v 358-360? How in such cases the minimum criteria would be met if there is no information concerning reporter? How could it be ensured that the report is not falsified?
	Could you please explain if reports from pregnancy, concerning misuse, abuse, overdose do not connected with adverse events should be classified as non-serious and reported like other non-serious reports in 90 days timeframe (v 501, 528)?
	Could you please clarify if in case of contractual arrangements the information described in v 565-568 must have the form of procedure or could be contained only within the agreement?
	Please provide more detailed clarification of situation described in v 709 – who will be authorized to decide if the medication error took place? Will the patient be able to state this?
	According to information contained in v 790-800 in case of compassionate use programs, may MAH decide whether the reporting of adverse events will be solicited or not?
	In case of literature articles (described in v 843) which detail patients in tables or line listings, concerning the substance for which PSUR is not required – should MAH submit it to the competent authorities? Where safety findings from these articles should be discussed (v 850)? Would the RMP be an appropriate document?
	In reference to v 947, could you please specify for how long after MA withdrawal collection of AE reports should be continued?
	In reference to v 961, could you please specify what does "large batch" exactly means? How many reports should it include?
	If the new version of MedDRA is released should all AE reports contained in the database be re-assessed? Or this should take place only in case of PSUR preparation?

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: In reference to v 316, we would like to highlight that it may be impossible to meet the 15-day deadline submission for serious reports obtained from the internet or digital media if the timeframes for expedited reporting are to be set basing on the date the information was posted. It is a quite realistic possibility that this kind of information will be found much later than 15 days from posting. Maybe it would be more appropriate to define day 0 as for literature reports? Proposed change (if any): The frequency of the screening should allow for potential valid ICSRs to be reported to the competent authorities within the appropriate expedited timeframe. The regulatory reporting clock starts as soon as the marketing authorisation holder has knowledge that the case meets the minimum criteria for expedited reporting.

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)

Comments from:

Name of organisation or individual
Teva Pharmaceuticals Europe B.V.

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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Duplicate check. There seems a lack of information in what is expected regarding duplicate checks. Before a case is reported to Eudravigilance – how will potential duplicates be identified? What if a report is sent to both the MAH and NCA/Other Agency?
	Definitions It should be absolutely clear earlier in the module that all **valid** reports non-serious **and** serious are considered 'expedited', it is only that the timelines are different. Currently companies associate the requirement for "expedited reporting" only with serious cases, and they could make assumptions that this is still has not changed. Suggest a definition of an expedited case earlier – e.g. under Section VI.A.2.6? And refer to VI.C.3 p 28 e.g. Expedited case = Any valid ICSR, serious or non-serious report. Serious to be reported in 15 days, non-serious to be reported in 90 days And also a definition of valid report, under Section VI.A.2.7? perhaps cross-referring to VI.B.2 p 11 e.g. A valid ICSR must contain the 4 minimal criteria.
	If a case is nullified from Eudravigilance, how will MAH be notified? There could be a number of cases which remain in the MAH safety database.
	Fore easier reference it would be helpful to provide the exact reporting requirements regarding patient reporting and non serious reporting in this 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')*
142		Comment: An event could be unintended but not necessarily noxious, e.g. a patient has suffered from tinnitus for many years and various standard treatments have made no difference; the patient than takes Product X for a completely unrelated indication, and the tinnitus stops. Proposed change (if any): suggestion for the update of the DIR: ".....noxious and/or unintended...."
165-169		Comment: The definition of misuse in the module is not identical to the definition used in the Annex. This causes confusion. Proposal: same definition in annex and module
168		Comment: Typo - subjects Proposed change (if any): Should be "subject"
193		Comment: "mutatis mutandis"' is too unclear for everyone to understand – please rewrite in English Proposed change (if any): The guidance in this Module also applies "*in principle, with appropriate changes where necessary,* " to medicinal products.....etc?
206-207		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 definition of a consumer does not mention carer - this would be a useful category to include Proposed change (if any): "....patient, lawyer, *carer,* friend, ..."
291-293		Comment: Is it the intention that the MAH needs to process only literature reports in which the author stated explicitly that the events are related to the administration of its products? What if such a statement is lacking? Proposal: clarification is needed.
310 - 332		Comment: the different sentences in this part are confusing. It should be better described that ICSRs received on websites which are company sponsored do require expedited reporting. Websites which are not company sponsored can be reviewed in order to confirm safety issues. Proposal: lines 322-329 refer to company sponsored sites. Lines 330-332 are redundant since 317-321 indicates that expedited reporting is not needed
317-321		Comment: This 'recommendation' to monitor special internet sites and patient support or disease area seems potentially onerous for generic companies who have many products often of wide-ranging therapeutic groups. Information on patientfora or disease sites do in general not generate important safety information. The amount of time to be spent on this is not in relation to the outcome. Those sites can however be helpful to investigate a potential signal or to confirm a signal but should not form part of any required monitoring programme Proposed change (if any): "It is also recommended that the marketing authorisation holder *and Member States* actively monitor special

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')*
		internet sites or digital media such as those of patients' support or special diseases groups, in order to ~~check~~ *confirm* ~~if they describe~~ significant safety issues"
340-348		Comment: Collection of individual non serious reports from clinical trials, PASS, named patient use, registries etc does not generate any relevant safety information for the safety profile of the product. These cases are present in the study database and are summarised in a final report. The benefit of individual reporting of non serious adverse reactions is not balanced with the huge workload and duplication of actions needed for these solicited non serious reports. Proposal: Indicate in VI.B.1.2 that this paragraph is only relevant for serious adverse reactions.
376-378		Comment: What is the exact definition of 'non-valid'? It is mentioned that these reports are needed for "ongoing safety evaluation activities" – but, if there is no suspect drug how could it be included in these activities? If only the therapeutic class is reported (for example – 'antibiotics') should it be entered as is? If no adverse event is reported, should the case be entered? If only the words 'adverse reaction' is reported, should it be entered as is? Proposal: The definition of 'non-valid' case should be further explained and it should be emphasised that cases without suspect drug or without events cannot be taken into account in ongoing safety evaluation activities.
400-401		Comment: As written in line 405-406 the burden for the reporter should be minimised as much as possible to assure the reporter also reports the next time. This means that asking the reporter for a written confirmation of the information as reported for example by phone is an example of avoidable burden to the reporter and will discourage the reporting of events. Company experience shows reporters do think this is a waste of their time and efforts. Only in case of adverse events for which follow up information is required could a form be sent and written

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')*
		follow up could be requested. Proposal: change the wording: … ~~Written confirmation of details given verbally should be obtained whenever possible.~~ *For ICSRs which are identified as requiring follow up this written follow up request* ~~routine pharmacovigilance activity~~ should be conducted…..
403-406		Comment: This suggests potential use of several targeted specific forms. Too many targeted specific forms could be very difficult to manage maintain and assess for complete information. Proposed change (if any): Add as appropriate. i.e. The use of targeted specific forms, if considered appropriate, should avoid the requirement to duplicate.....
435		Comment: Who are the stakeholders (this term has not been used before) that are referred to? MAH, EMA, CAs, co-licensee, co-marketing partners, etc? Proposed change (if any): Define what is meant by stakeholders.
435		Comment: "Case report information should only be transmitted between stakeholders in an **anonymous** format". If the stakeholders referred to includes third party companies who are marketing the products of the MAH, and the reports are received in anonymised form then the MAH will not be able to follow-up the reports. Proposed change (if any): Suggest include:"If a third party company is marketing the product of an MAH, the third party company should

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')*
		request and endeavour to obtain documented permission from the reporter for the MAH to contact the reporter direct, or they should advise the reporter who the MAH is and provide them with contact details to enable them to report to the MAH direct.
452		Comment: Refers to regulatory organisations. How does this differ from NCAs and the Agency? The phrase is used again later (line 478 – but not again at all). Proposed change (if any): If this phrase's meaning differs from NCAs and the Agency, this should be made clear. Suggest add definition of NCAs and Agency to Annex 1 Definitions? If it doesn't differ then why use it?
476		Comment: This indicates that pregnancy reports should be followed up on the outcome of the pregnancy and the development of the child. It is not relevant for every pregnancy report to follow up the development of the child – especially since there is no definition for child. A risk based approach should be taken on the possible impact on the development of newborns or toddlers. It should only be undertaken when described as an additional pharmacovigilance measure in the Risk Management Plan. Proposed action: Replace "child" by "newborn"
533		Comment: Reporters should not be unnecessarily burdened with follow up requests. Follow up should only be undertaken if relevant from a medical or pharmacovigilance point of view Proposal: *If medically relevant,* they should be followed-up
557-561		Comment: This paragraph suggest that reports received by contractors for competent authorities are not considered to 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')*
		day zero. Proposal: …. national or regional pharmacovigilance centre of a competent authority , *including their contractors*, or of any personnel of he marketing authorisation holder……
584 - 586		Comment: "Where an initially serious case is downgraded the FU information should still be reported on an expedited basis within 15 days" This only refers to situations where an initial serious cases is reported to Eudravigilance. If the case is still in the initial processing phase there is no need to report the case in 15 days. Proposal: Where an initially serious case*, which has been reported to the Eudravigilance either by the CA or the MAH,* is downgraded to non–serious…
649		Comment: Typo. "The reporting rules of solicited reports to the EudraVigilance database modules are dependent **of** the types of organised collection systems." Proposed change (if any): The reporting rules of solicited reports to the EudraVigilance database modules are dependent *on* ~~of~~ the types of organised collection systems.
660 + 664		Comment: The reporting of CT events depends on the 'nature of the intervention'. This should direct the reader to what this means. Proposed changes (if any): *Because they are* ~~Due to the nature of the~~ intervention*al*
715-717		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')*
		"Unless there are justifiable grounds resulting from pharmacovigilance activities, individual Member States shall not impose any additional obligations on marketing authorisation holders for the reporting of suspected adverse reactions." What would be **justifiable** grounds for an individual MS to impose additional obligations?. This gives ground to individual interpretations. Such practices needs to be harmonised amongst NCAs Proposed change (if any): Add: additional obligations may not be imposed unless endorsed by the PRAC
732-741		Comment: " or any company not belonging to the same company or group of companies but having concluded commercial agreement with the company..... Commercial agreement is too broad – it can be an agreement for supply of API, contract manufacturing or regulatory intelligence. It should be specified that this means co-marketing agreements.
750 + 763		Comment: Collection of individual non serious reports from clinical trials, PASS, named patient use, registries etc does not generate any relevant safety information to the safety profile of the product. These cases are present in the study database and are summarised in a final report. The benefit of individual reporting of non serious adverse reactions is not proportionate to the huge workload and duplication of effort needed for these solicited non serious reports. Proposal: Indicate in VI.C.2.2.2 that expedited reporting is only relevant for serious adverse reactions . Non serious reactions will be summarised in the final report collection.
822-828		Comment: Is there a timeline to agree the list of active ingredients and journals that will be monitored by the Agency?

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')*
831		Comment: Marketing authorisation holders should also make themselves aware of publications in local journals. Will the local CA provide guidance which additional local journals are required to be monitored?
860		Comment: VI.C.2.2.4 Suspected adverse reactions related to quality defect or falsified medicinal products. It is important to include if possible the origin of the suspected falsified medicine in the ICSR report eg. Since it is essential for public health reasons to understand where the falsified product was bought (eg. Via Internet) or purchased illegally from outside EU or to know whether it was bought from local pharmacy.
931-933		Comment: Literature searches for generic products from submission until approval are unnecessary and excessive. Proposed change (if any): Ensuring that the SmPC is in line with the reference product SmPC, at the time of submission, and if appropriate following referrals during assessment, is more appropriate.
949		Comment: How long after withdrawal or revocation of an MA should monitoring continue? Proposed change (if any): Suggest include monitoring until the last batch of product has expired.
1008-1009		Comment: Cases should only be made available to the relevant MAHs Proposal: …also make available to the *relevant* marketing authorisation holders of the suspected…..
1010		Comment: Interim process. Non-serious reactions should be reported 'if required' to the CA in the country of occurrence. What do they

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')*
		mean by 'if required'. This opens the door for inconsistency between MS. Proposed change (if any): the requirements of each CA should be available on the agency's webportal as soon as possible
1193-1198		Comment: Capturing data only in the narrative and not in structured fields is problematic for data retrieval purposes. Such cases cannot be retrieved and will be lost for analysis. Even if only the product class (for example: SSRIs) is available, it can be retrieved in certain scenarios. Therefore it should be allowed to use a structured field for a therapeutic class
1356		Comment: for the additional pharmacovigilance activities as needs to be done in an Risk Management Plan of the MAH, it can be very important that translated information is made available to the MAH. Proposal: … when requested by the Agency, *the marketing authorisation holder or* other Member States….
1369		Comment: Why "maintain" a duplicate case in the ICSR database? This could lead to further duplicates if not managed correctly. Proposed change (if any): Consider replacing "maintain" with "retain".
1538		Comment: This is not possible. If a case is distributed internally or between companies as non serious and is considered serious by the receiver the receiver should be able to change the seriousness of the case or to add/correct coding to assure better quality data.

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: Lines 1538-1539 should be deleted
1576		Comment: An initial case should be validated without the batchnumber – otherwise if for whatever reason the batchnumber is not available the case will never get into the database. Proposal: Correct the flow
1627 - 1638		Comment: Upon reading this section it is not clear what message is being conveyed. It appears to read as a point of fact rather than guidance. What is the intention of mentioning this? Proposal: clarify or delete
1655		Comment: The requirement for searching literature for excipients with pharmacological effects is mentioned. As there is guidance already available for excipients with known pharmacological effects, will it be necessary to involve such excipients in routine literature searches. It should be clarified that this is only needed when the the excipient is present in amounts that are pharmacologically active. Proposed change (if any): …..can include excipients and adjuvants*, in pharmacologically active amounts,* that may…..
1712		Comment: "Full citation....should always be retrieved and reviewed" – This could be extremely costly for companies. Also, for a safety article why would the complete paper be needed if an informative abstract is available containing

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')*
		sufficient information to constitute a valid report and allow reasonable assessment i.e. in the case of a generic product. Proposed change (if any): Full citation is only needed if the minimum four data elements and a reasonable assessment of the case is not possible from the abstract, or no abstract is available. Full citation is only needed if a PSUR is to be submitted for the product or a potential safety issue is identified.
1716 - 1717		Comment: "qualified to identify the article of relevance" – What does "qualified" mean? Proposed change (if any): Replace "qualified" by "*Experienced and/or trained*"
1749 - 1753		Comment: "check to prevent reporting of duplicates" - this is easy on the internal MAH database. How will this work for checking of duplicates reported via other routes? For example a doctor reports to the MAH, the pharmacist reports directly to the EMA and the consumer reports to local CA; none of them checks with/or informs the other that they are reporting this case.
1821		Comment: Title not clear Proposed change (if any): Expedited reporting of suspected adverse reaction in the EU – interim arrangements.
1881		Comment: What happens if a case is nullified by the Competent Authority ("sending organisation") – how will the MAH find out about this?

Please add more rows if needed.

<Date of submission>

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

Comments from:

Name of organisation or individual
Medicines and Healthcare products Regulatory Agency

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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The document does not contain any guidance on handling ICSRs from market research programmes. It may be useful to review the ABPI guidelines on this topic (e.g. training of Vendors used, method of reporting etc.).	
	The document contains a lot of detail about literature searching (including common inspection findings) and whilst this detail is helpful, it is noticeable that other sections in comparison are far less specific.	

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')*	Outcome *(To be completed by the Agency)*
185		Amend to Directive 2001 and not 2011	
187-192		Comment: The assumption of this statement is that the scope includes the reporting of adverse reactions by the MAH of any medicinal product that is licensed outside the EU that contains the same active substance that is licensed within the EU irrespective of the product itself. Therefore, an active substance that is a nasal powder outside the EU should be reported on an expedited basis if the same MAH held a marketing authorisation for an injectable product containing the same active substance within the EU. Proposed change (if any): It would be useful to clarify the legal basis for this requirement as this represents a significant change from current legislation and guidance.	
227		Comment: It would be more appropriate to refer to the patient or consumer as opposed to "subject".	
232		Proposed change (if any): recommend change "of the cases" to "ICSRs". Recommend removal of "in the framework of day-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')*	Outcome *(To be completed by the Agency)*
		day PV activities" as this is non-specific.	
254		Comment: It is unclear what is meant by "consistent" in this context.	
256		Comment: Recommended to add "and also in accordance with the record retention timelines stated in the Commission Regulation on Implementing Measures".	
268		Comment: A spontaneous report could be derived from an organised data collection scheme (see line number 801 below).	
272-273		Comment: This statement could cause confusion as a patient/consumer could also report an adverse event/reaction that is not spontaneous e.g. in the context of a market research programme, patient support programme etc. HCP confirmation and report type are separate concepts and should not be linked.	
284		Comment: What does company office mean? Does this mean each territory where the MAH has a specific office, each territory where the MAH holds a marketing authorisation? The way the guidance is written now seems to indicate non-EU offices should be looking at local journals. Is this what was intended?	
284		Proposed change (if any): add "scientific" after local.	
287-290		Comment: The sentence suggests that the MAH should not process and collect ICSRs arising from interventional clinical trials that are identified from literature (e.g. from trials not sponsored by the MAH). The MAH may identify ICSRs from an	

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		interventional clinical trial that the MAH did not sponsor and that was conducted outside the EU by a sponsor who is not running trials with the same product in the EU. In which case there may be no obligation for any party to report such ICSRs to the EU authorities. Is this what is intended? However, the MAH should still consider such information for the purpose of ongoing safety evaluation.	
289-290		Comment: It may be beneficial to include the fact that recording ICSRs from the literature should be irrespective of seriousness or Listedness as some MAHs have in the past not record, for example, non-serious listed ICSRs from this source.	
292-295		Comment: This is unclear. This statement may fit better in section VI.C.2.2.3. or this sentence should be clarified. Does this mean the MAH should consider such reports (even if they have not commercialised the product in the territory?) or can rule out such reports as not relating to their product?	
293		Comment: If the author(s) include no information about causal relationship, should the MAH assume a causal relationship, but at the same time attempt to follow-up to obtain this information?	
310		Comment: It would be useful in this section to provide detail on what is acceptable with regards to the method of how MAHs should screen digital media. Would targeted searches of lengthy blogs ever be appropriate / risk-based approach to screening based on product specific identified and potential	

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		risks etc? Will further guidance be provided on this topic? In addition, it may be useful to provide guidance on how MAHs should set up websites in order to make it easier for ADRs to be reported directly, rather than just posts on a blog.	
313-319 and 326-328		Comment: These two paragraphs appear to give slightly different guidance on what is expected of MAHs with regards to non-company sponsored websites: The first paragraph says that MAHs are only recommended to monitor these sites for significant safety issues that could warrant reporting as emerging safety issues – however the final paragraph says that any report of a suspected ADR identified on non-company sponsored websites should be assessed for eligibility for expedited reporting (i.e. so not just those that represent significant safety issues). In light with the new requirements for the reporting of non-serious events – there could be a lot of reports that are identified for expedited reporting not just the significant safety issues….	
317		Comment: From an inspections point of view, this is too vague to be considered an inspection finding. It would be impossible to know which particular sites a company should monitor based on their particular product portfolio. It is recommended that this part is removed unless it is definitively a	

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		recommendation only.	
327		Comment: This is unclear. Is the patient identifiable if the email address is valid or do they have to confirm their details via an email address? If you do not get an "undeliverable" message is that email address considered valid?	
329		Comment: This is unclear. What is the source country? Where report is received or where review took place? This could be different.	
333 - 339		Comment: Some reports from patient support and disease management programmes can be spontaneous. This contradicts the guidance in lines 813-816. In some patient support and reimbursement programmes, spontaneous ADRs are collected i.e. the patient contacts the programme to spontaneously report an event. If the programme covers most of the population that receives the drug, then a high % of spontaneous reports might be received via this route. Perhaps this sentence should be deleted, because EU-specific guidance (which is different) is provided later on?	
338		Proposed change (if any): amend to patient compliance.	
341		Comment: Who should make that causality assessment?	
349-356		Comment: This paragraph is confusing. It says that an identifiable reporter must have contact details but then goes on to say that if the reporter doesn't want to give them the report should still be valid. This paragraph could be simplified	

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		to say that whenever possible contact details for the reporter should be obtained so that follow-up activities can be performed however if the reporter does not wish to provide contact details this should not have an impact on the validity of the reporter as long as an identifier (qualification, initials etc.) has been provided.	
357-8		Comment: What are the implications if initial reporter is identifiable but subsequent ones are not? Is the new information not valid and therefore not reportable? This sentence could be misinterpreted.	
407		Comment: By specifically referencing serious reports in line 407, some readers may infer that non-serious reports do not have to be followed up. However, it may be important to follow up non-serious reports e.g. if they relate to events of special interest that are being actively monitored; in order to obtain HCP confirmation; if the report is missing information which may affect the seriousness classification.	
414		Comment: If the patient or consumer is not willing to provide consent to contact a healthcare professional should the MAH attempt to obtain further information from the patient or consumer themselves? When requesting written HCP consent should it not be recommended for the MAH to request any additional information not provided at the time of initial reporting e.g. over the telephone?	
435		Comment: The term pseudo-anonymised is used later in the GVP and may be more appropriate.	

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437		Comment: By on-line accessibility does this mean continual access to data? This is unclear. On-line access may not be necessary for a small MAH who holds a handful of ICSRs on file. In addition, why do data have to be stored in a way to ensure electronic reporting of ICSRs? Surely the MAH can store the data in the best format for their needs, as long as they can also fulfil electronic reporting requirements?	
439		Comment: This sentence is confusing. What does "monitored" and "validated" mean in this context? Should the use of appropriate selection of terms be subject to quality control, quality assurance auditing or both?	
441-443		Comment: This sentence is unclear. Proposed change (if any): Perhaps amend to "Data from the primary source should not be altered, filtered or modified during electronic transmission and the original verbatim text or an accurate translation of it should be included.	
454		Comment: Recommend amending this list to follow a logical order e.g. archiving should be last in this list of activities.	
465-469		Comment: This guidance could be counter-productive. In most cases non-PV staff only need to know how to collect PV data and forward this to the PV dept. Training them in PV legislation and guidelines might lead to confusion and possible unwarranted filtering of reports if PV is not their primary role.	
489		Proposed change (if any): Change "structure" to "structured".	

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500		Proposed change (if any): Change "on" to "in".	
503		Proposed change (if any): Change "to the marketing authorisation" to "**of** the marketing authorisation".	
538		Comment: How should MAHs handle such reports where neither a PSUR or risk management plan exists for the product in question?	
540		Proposed change (if any): Change "days" to "day".	
541		Comment: It would be useful to extend the examples to include drugs used in anaesthesia and critical care. Lack of effect in paralyzing agents and IV sedatives can very easily lead to fatalities or life-threatening situations when intubating or maintaining a patient on artificial ventilation, lack of efficacy in cardiac inotrope infusions (adrenaline, dobutamine, noradrenaline etc) can lead to catastrophic falls in blood pressure with similar consequences.	
562-567		Comment: Day 0 for cases received from Licensing partners and distributors is covered in lines 738 to 741, but not in this section.	
578		Proposed change (if any): Change "cases" to "case".	

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591		Comment: "High quality" is unclear in this context.	
630		Comment: As highlighted previously, if the MAH is sponsoring interventional clinical trials outside the EU, but is not sponsoring any trials with the product in the EU, then there is gap, as there is no requirement for the MAH to expedite SUSARs from these trials to EU authorities under either Directive. However, the results from these trials should still be discussed in PSURs (if PSURs are still required) and should be considered as part of ongoing safety evaluation.	
637		Comment: "impact of the risk-benefit balance" should read "impact on the risk-benefit balance". In some GVPs the form "benefit-risk" is used instead of "risk-benefit". There should be consistency across the GVPs.	
708		Proposed change (if any): Change to Eudra**V**igilance.	
718 and 725		Proposed change (if any): Change "holders" to "holder".	
727		Comment: It would be useful to also include pharmaceutical form in this exclusion list.	
732-741		Comment: This paragraph is unclear. Suggest re-wording.	
801		Comment: The section on patient support programmes should be made more detailed and clearer. It may be useful to include a flow diagram to demonstrate 1) how PSPs can be designated as solicited or spontaneous, 2) under what circumstances they are HCP confirmed (especially if the PSP is	

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		administered by nurses etc), 3) what the requirements are in terms of company assessment and follow-up and 4) whether they should be expedited, appear in study reports etc. Fundamentally, a PSP is not primarily set up to generate and collect data.....; they are set up principally to provide education and assist the patients receiving the drug in terms of re-imbursement, patient compliance etc. As a consequence safety data will become available. This section confuses the category of organised data collection scheme (ODCS) and patient support programme. All ODCSs are not always PSPs. Surveys, information gathering may or may not be part of a PSP or could be a market research programme or other study; this should be made clear. This section is unclear as to how to handle a solicited consumer report where the consumer has not mentioned causality. Can the MAH assess the report and if this is considered not related not expedite? The solicited example could be improved. It is far more likely that the MAH contacts a patient or HCP involved in a programme to see how the treatment is going in general - i.e. has the patient managed to take all their doses when required? If the answer is no, because they experienced an ADR, this can be regarded as solicited. If a company is contacting patients / HCPs and asking about ADRs / outcomes specifically, this would generally fall into the "research" category - a distinction should be made between these activities and PSPs.	

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		The spontaneous example, in our view is not a spontaneous report as the MAH has contacted the patient/HCP – the reporter has not contacted the MAH spontaneously to report the information. A common scenario seen is where the MAH contacts the patient / specialist pharmacy to confirm whether drug needs to be shipped (e.g. as part of a reimbursement programme) and is informed that this is no longer needed as the patient has died / stopped treatment for a specific reason / had an AE/ADR. Examples following this line are far more useful but in our view represent solicited and not spontaneous reports. An example of a spontaneous report could be where the patient/HCP contacts the MAH via the medical information service or dedicated PSP phone number provided to report information at their own accord, not if the company has contacted them. Another scenario that could be covered is where the MAH is contacted by a patient or HCP to report the fact that no further drug needs to be provided (e.g. if the MAH is providing free or reduced cost drug in prescribed circumstances). It would be important to determine why AEs are being reported in this context (if possible). For example, are they phoning up to report an ADR spontaneously, are they phoning up to say they have discontinued product because of an AE related to the product in question or are they phoning up to say they now have condition X which makes them unsuitable for	

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		treatment or a better treatment regime is available? Or is it that the patient has died (which may be related or unrelated to treatment)? A flow diagram would be extremely helpful for this section.	
835		Comment: Same comment as line number 727.	
835-838		Comment: With reference to 21 March 2011 EMA/46003/2011 EudraVigilance Expert Working Group (EV-EWG) EudraLex – Volume 9A – Questions and answers on implementation Version 5.4 the Pharmacovigilance IWG discussed the following ID numbers (12, 38 and 55). In summary, the general consensus was that guidance should give further detail on when a MAH cannot exclude the product on the basis of territory. It is recommended that guidance state that MAHs report ICSRs arising in the literature from territories where there is no MA, unless the company can demonstrate that the product has never been placed on the market in that territory and the product is not a travel medicine. This is to ensure that where the MAH has knowingly supplied their product to territories where it does not hold a marketing authorisation that these ICSRs are captured appropriately. For example, since MAs often are not in place in e.g. African countries, but product is still placed on the market via distributors. Hence, legitimate ADRs could arise from these territories and remain otherwise unreported.	

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		Exclusion from expedited reporting is more difficult to define for territory considerations, but could include proof that the company has never placed product on the market in a specified territory, however, the caveat is required for travel medications.	
843		Comment: If all criteria for a valid case are present but only in the table / line listing format it is assumed this need not be expedited? What if the patients are described in the text and data are also summarised in a table? We believe this needs further qualification.	
857		Comment: This guidance was developed by MHRA. Perhaps the words "by the Agency" should be omitted.	
862		Comment: #1 What would the product details be for a confirmed falsified medicine - what the counterfeit is claiming to be? This should be made clear - VI.C.6.2.3.5 does not really clarify this. If these cases have to go into databases as valid cases with same product details as genuine product in order to report as an ICSR, care is going to be needed when searches are run for signal detection PSUR etc. #2 Does a counterfeit/defective medicine report need to have all other validation criteria? (the sentence does not make it clear).	
927		Proposed change (if any): Include "update" in "periodic safety report".	

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931-933		Comment: It would be useful to clarify that this includes significant information from the published literature.	
939-942		Comment: It is unclear why a MAH should report in this circumstance. The MA may never be granted and this has resource implications (particularly for new MAHs not yet present in the EU) for potentially no gain in knowledge (particularly if the MA is not granted in the EU). Whilst the terminology "should" is utilised, it is felt that "recommended" would be more appropriate. Would an update report on ICSRs from outside the EU provided to the Assessor at final determination not be more appropriate prior to MA grant in this scenario?	
942		Comment: Would additional safety data from interventional clinical trials that the applicant is conducting outside the EU have to be provided under some other requirement relating to marketing applications (if no trials are being conducted in the EU)? There is a potential gap and inconsistency in reporting these data versus spontaneous data.	
948		Proposed change (if any): Remove "for example".	
956		Comment: It would be useful to include guidance on what level of information is expected to be included in ICSRs in the scenario where hundreds of pages are provided to the MAH on one patient. This could do with more clarity. Do we want to	

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		report only the events reactions alleged by the class action or the alleged events PLUS any other incidental adverse reactions concerning the drug in question gathered from any supplied medical records? i.e. are MAHs expected to trawl medical records for any adverse reaction associated with the drug or just those adverse reactions which are being alleged in the lawsuit? At large companies a vast amount of resource could be wasted if this is not clear.	
974		Proposed change (if any): Please correct, this only applies to non-serious reports that occur in the EU (see Article 107(3)).	
1028-9		Comment: What is meant is not all ICSRs that occur in their territory (because MAHs will already have reported some of these directly to EV), but ICSRs that occur in their territory that are directly reported to the NCA e.g. by patients and HCPs. The same comment applies to 1033-4.	
1099-1111		Comment: There is good guidance in the GVP of when to use the report types of spontaneous and report from studies – however there is no definition of when to use the report types 'other' or 'not available to sender (unknown)' The definitions are also not included in the EudraVigilance guidance document that is cited.	
1294		Comment: It is unclear whether this piece of guidance requires review by a medically qualified person of all follow-up cases? Can a non-medically qualified person provide medical judgement? This needs to be clear. It is noted that line 226	

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		refers to medical and scientific judgement when referring to seriousness assessment.	
1302		Proposed change (if any): Include "not" after "may".	
1310 and 1319		Proposed change (if any): Change "typos" to "typographical errors".	
1392-1395		Comment: Should the route of administration be captured as 'other' as the route is known but is not available for selection?	
1482		Proposed change (if any): Refer to events / reactions as singular.	
1484		Proposed change (if any): Change to reactions.	
1586		Proposed change (if any): Change "report" to "review".	
1585-1588		Comment: It is proposed that the guidance is made clear that this could be performed periodically and a weekly requirement is not necessary in this situation.	
1589		Proposed change (if any): Delete "would" and change "include" to "includes".	
1590		Comment: It is proposed this states "periodic" literature searching for clarification purposes.	

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1596		Comment: It is proposed this states that literature searching on a periodic basis should commence after MA submission and become a weekly activity post MA grant.	
1605		Proposed change (if any): Change "finding" to "identifying".	
1669		Comment: It would be useful if this section included common search terms that should be selected (as a non-exhaustive list) to help guide MAHs. The same information could be put in different terms such as "The selection of search terms should be such that the following are included..."	
1720		Comment: It is recommended that quality control checks are performed on a sample of literature reviews / selection of articles to check the primary reviewer is identifying the relevant articles.	
1721		Comment: The referral to inspection findings in this area is not consistent with the rest of the document.	
1731		Comment: This list should be identical to previous reasons for excluding the MAH's product.	
1749-1753		Comment: It is unclear what this section means. How do MAHs check literature cases to prevent duplicate reporting?	
1824		Proposed change (if any): In No. 3.1 change "got so" to "go to".	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

Comments from:

Name of organisation or individual
United Biosource Corporation

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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Use of the term risk-benefit: Could the EMA revert to using the term benefit-risk in all its regulatory documents? Rationale: The use of benefit-risk is in line with ICH, CIOMS and terminology used by all the other regions. Also it makes it easier to make clear and unequivocal statements such as 'the benefit-risk of the product remains positive' in the context of benefit-risk assessments. Additionally, a recent update of the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') made use of the term benefit-risk throughout. This approach is welcome.

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')*
132 - 134		Comment: It seems EMA is creating a two tier regulation, where requirements within the same GVP document have different weights/importance. EMA to confirm may be the real implications of the use of shall and should within the same regulatory document. Have never encountered this approach before in any pharmaceutical regulatory text. EMA to confirm if there is a two tier approach within GVP and what are the real-life implications of the use of 'shall' versus 'should' in terms of compliance and inspections. Proposed change (if any): Please remove this approach.
193 - 196; 790 - 800;		Comment: The proposed approach may have major implications for products that do NOT yet have a Marketing Authorization (MA), but may have Name Patient Programs (NPPs) or compassionate use programs in place. Consequently, it may have major implications for start-up companies who may be submitting a first Marketing Authorization Application in the EU. Proposed change (if any): Please consider introducing a two scenario approach, as follows: Scenario 1: safety data arising from NPPs/compassionate use programs for products that do not have a MA in the EU, then reporting should be done according to Volume 10, even if there are no ongoing interventional CTs. Scenario 2: For products that have a MA in the EU, then safety data can be handled as per GVP. Rationale supporting this proposal: Clarity regarding safety reporting arising from NPPs/compassionate use in the EU; will lead to a more harmonised approach in the EU; will streamline safety reporting for NPPs/compassionate use programs according to their marketing status in the EU; will align better with US FDA requirements/legal framework for safety reporting in the context of NPPs/compassionate use which in US is to be treated as safety data arising from CTs. From a regulatory perspective this also makes sense as where there is a MA in the EU patients in NPPs/compassionate use are automatically classed as off-label use. Whereas for a product with no MA in the EU all use is by definition off-label and therefore Volume 10 should apply.

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284 - 286		Comment: The use of the term 'encouraged' (as opposed to the term 'expected' used in the context of global literature searches), leads us to conclude that weekly local literature searches are not mandatory. Proposed change (if any): Please use clear language which will allow for greater harmonisation of requirements in the EU and to MAs being able to clearly meet their obligations concerning local literature searches.
296 - 297		Comment: Definition of clock date not consistent with page 17 Proposed change (if any): Please amend relevant sections for consistency.
317 - 332		Comment: Taking into account how the world wide web operates, this requirement seems not reasonable. Proposed change (if any): Please amend this section as follows 'MAHs should monitor and collect data from websites they sponsor or control. Monitoring of non-company sponsored/controlled websites may be required on a case by case basis (e.g. risk management of psychotropics). Such a requirement will have a well founded rationale and be documented in the risk management plan.'
327		Comment: We disagree with this approach. Valid email address should not be considered as identifiable reporter and is not consistent with definition provided on page 11 (line 353 to 358) Proposed change (if any): Remove valid email address as an identifiable reporter. If removal is overruled, then please amend relevant sections for consistency.
335 - 338		Comment: 'Compassionate use' needs to be added to be consistent with page 23 line 756 Proposed change (if any): Please amend relevant sections for consistency.
583 - 584		Comment: Not consistent with definition in page 17, line 557-561. Proposed change (if any): Please amend relevant sections for consistency.
787 - 789		Comment: Yet again, the EU refers to local requirements which differ immensely. Proposed change (if any): Suggest that the concept of a CEC is used for reports of non-interventional trials where

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		all this information is centralised so that MAHs need only submit one report to each country CEC. Rational supporting proposed changes: the CEC network is already in place for interventional clinical trials, therefore it would make sense to use this resource; decrease the reporting burden so that MAHs can concentrate on safety data analysis and therefore in real patient protection; EU harmonisation for reporting in non-interventional trials.
943 - 949		Comment: It is not clear for how long after withdrawal of a MA in the EU the surveillance activities should continue and who should carry them out in case the MAH no longer exists (e.g. went into liquidation). Proposed change (if any): Would be helpful if there were clear and harmonised provisions covering the points raised above.
973 - 975		Comment: Further clarity desirable due reporting timelines issues. Proposed change (if any): To be udpated as follows: serious valid ICSRs , from HCP or non-HCP, shall be reported by competent authorities in Member States or by marketing authorisation holders within 15 days from Day 0/clock date. Non-serious valid ICSRs, from HCP or non-HCP, shall be reported by competent authorities in Member States or by marketing authorisation holders within 90 days from Day 0/clock date.
999 - 1000		Comment: Unclear whether requirement to report to the reference member state (RMS) for MRP/Rapporteur for CAP still stands. Proposed change (if any): Please confirm if additional reporting to the RMS and Rapporteur still applies.
1001 - 1004		Comment: For harmonization purposes, reporting should be done exclusively to Eudravigilance and the member states should access such cases from there. Proposed change (if any): Please delete "If required, those reports shall also be reported to the competent authorities in the Member States in which the medicinal product is authorised."
1005 - 1009		Comment: Some Competent Authorities in some Member States are not able to forward the ICSRs they receive to

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		EudraVigilance (e.g. Cyprus) and they ask MAH to do so. Proposed change (if any): Please implement a text that imposes clear mandatory requirements for Competent Authorities to ensure harmonization.
1011 - 1013		Comment: This is an unreasonable requirement, due to the burden it creates to companies who should be concentrating on analysing safety data and risk minimisation activities rather than dealing with logistical matters due to apparent unwillingness to harmonise. Proposed change (if any): Please implement a text that imposes clear mandatory requirements for Competent Authorities to ensure harmonization.
1291 - 1295		Comment: Inconsistent with line 575-578 in page 17. Proposed change (if any): Please amend for consistency.
1338 - 1340		Comment: This is a complex area, where it would desirable to have some leadership from the HMA in trying to at least collate the differing requirements. Proposed change (if any): Due to differing and ever changing requirements throughout the EU, it would be helpful if member states compiled an appendix highlighting which member states have data protection laws different to the ones established by the EU directive on data protection. The HMA could lead on such an initiative.
1493 - 1499		Comment: This is unreasonable and may be misleading. Some Competent Authorities/Agency could assume that the MAH had been non-compliant as the only way for them to know why the case was not submitted within 15 days from Day 0 would be by looking at the narrative which will explain that the case was initially non-valid. Proposed changes (if any): Please modify as follows 'Date report was first received from source should be date on which the report became valid. '
1605 - 1610		Comment: This excerpt of the guideline suggests that it may be advisable to perform a regular review of 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')*
		database that has a less clinical focus and includes more laboratory-based publications. We consider that the major databases cited (Medline, Embase and Excerpta Medica) include sufficient non-clinical information. Proposed changes (if any): Please remove this suggestion.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<18 April 2012>

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

Comments from:

Name of organisation or individual
vfa (Association of Research-Based Pharmaceutical Companies), Germany

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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	There is a lack of guidance for Market Research.
	Duplication of definitions should be avoided wherever possible, and ideally definitions should exclusively be maintained in the GVP Annex "definitions".

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 164-165		Comment: Misuse definition slightly unequal to misuse definition of the GVP annex (Definitions) in line 223. Original text in line 223 of the annex: "...the indication(s) or **not** within the legal status...". Whereas the original text in GVP module VI: "...the indication(s) or within the legal status...". Proposed change (if any): Harmonisation proposed.
Line 280-281		Comment: It is stated, that "all company offices are encouraged to be aware of publications in their local journals". Rationale for a proposed change: Screening for <u>all</u> products in a company at a local site in local journals is a large work load. Therefore it should only include products that have a marketing authorisation in that country. Proposed change (if any): In addition, all company offices are encouraged to be aware of publications in their local journals for medicinal products that have a marketing authorisation in that country and to bring…
Lines 289-291		This also applies to reports identified in the scientific and medical literature that originate in a country where a company holds a marketing authorisation but has never commercialised the medicinal product. Comment: This requirement contravenes the principle spirit of the management of literature articles in that duplicate reporting by different MAHs should be avoided. An adverse reaction occurring in a particular country will be reported by the MAH who markets the product in that particular country. Therefore a separate MAH who has never launched the product (and may never launch it in the future) should not *report* the article about an ADR

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')*
		which occurred following administration of another company's product to avoid case duplications. We understand that weekly literature searches will need to be conducted in the interest of signal detection independent of the below proposal. Proposal: The above quoted sentence should be deleted. .
Lines 317-321		Comment: Significant concern regarding actively monitoring of unsponsored internet site resulting in a significant workload and poor added benefit. Proposed change (if any): EMA and national competent authorities should post on their authority website that special disease patient groups are encouraged to report adverse reaction identified on their sponsored websites to the competent authorities or the marketing authorisation holder.
Lines 336-338 + 745-746 + 766-768 + 801-804		*For the purpose of safety reporting, solicited reports should be classified as study reports, and should have an appropriate causality assessment, to consider whether they meet the criteria for expedited reporting.* *Marketing authorisation holders shall record all reports of suspected adverse reactions originating from within or outside the EU, which occur in post-authorisation studies [DIR Art 107(1)].* *Only reports of adverse reactions where a possible causal relationship with the suspected medicinal product is considered by the primary source* ***or*** *the marketing authorisation holder should be reported; other reports of events should be included in the final study report*. 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')*
		Lines 336-338 define reports from non-interventional studies as study reports, requiring appropriate causality assessment. Lines 745-746 require ADRs to be recorded in post authorisation studies. The word "or" in line 767 seems to suggest that AEs must be collected in non international studies, so that a MAH causality assessment can be performed in order to identify expeditable cases. Is this the intension? Or would it suggest that only if AEs are collected then a MAH causality assessment must be performed? Does the causality assessment of the primary sources otherwise suffices? In chapter VI.C.2.2.2.3. patient support programme one paragraph is as follows: ***Adverse events may be actively sought*** *during the conduct of these types of organised data collection schemes, in which case they should be considered as solicited reports. Only reports of adverse reactions where a possible causal relationship with the suspected medicinal product is considered by the primary source or the marketing authorisation holder should be reported.* Comment: The requirement that "AEs may be actively sought" here is clear whereas in the case of non interventional trials it is not clear.
Line 491		Comment: Classification of serious reports in pregnancy cases: "reports of congenital anomalies or developmental delay..." This assumes that a new serious criteria (developmental delay) is added but not added to the definition of seriousness thus not aligned to GCP Annex (Definitions, lines 374-377) and to line 218 of GVP module VI This addition of a serious criteria is a potential risk for late reporting. 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')*
		Please delete "developmental delay" in order to harmonise the definitions.
Line 510		The phrase "Every attempt…" is too strong in this scenario. Proposed change to line 510: *Every attempt* ***Reasonable attempts****…* Additional comment about the following GVP text: The collection of safety information in the paediatric or elderly population is important. Every attempt should therefore be made to obtain and submit the age or age group of the patient. The wording implies that in all instances when a spontaneous report is received without specification of the age/age group follow up attempts have to be made to obtain such information. Stratification of safety information per age groups has the objective to identify new age-group specific adverse events, differences in the nature of known adverse events, long term effects or new information on under- or over-dosing. The proposed wording would make it mandatory to seek for follow up even for well known non-serious adverse event reports if no age information is provided. This is inappropriate use of resources and neither in accord with the recommendations of CIOMS Working Group V for follow up approaches nor requested in the Guideline on Conduct of Pharmacovigilance for Medicines used by the Pediatric Population (Doc.Ref.EMEA/CHMP/PhVWP/235910/2005- rev.1.) Proposed wording: The collection of safety information in the paediatric or elderly population is important. Reasonable attempts should therefore be made to obtain and submit the age or age group of the patient. For such safety reports where neither information on age or the age group of a patient is provided careful medical consideration should be applied to decide whether follow up has to be sought to obtain such 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')*
Lines 527-532		GVP text: Reports (of overdose, abuse, misuse, medication error or occupational exposure) associated with suspected adverse reactions should be subject to expedited reporting. They should be routinely followed-up to ensure that the information is as complete as possible with regards to symptoms, treatments and outcomes. Comment: The decision whether or not further follow-up is required should be made after careful medical evaluation for each individual case. Such evaluation should follow a risk-balanced approach. In cases entailing relevant overdose sequelae (for example coma) the MAHs will have a high interest in obtaining as much follow up information as possible. Reversely, it does not add value to collect follow up only for completeness sake in cases with acknowledged and typically transient (self-limiting) adverse sequelae of an overdose. Accordingly the request to conduct follow up on every case in the above categories as a routine without applying a risk balanced approach is against the spirit of focussing pharmacovigilance on what is relevant. Proposed wording: Reports (of overdose, abuse, misuse, medication error or occupational exposure) associated with suspected adverse reactions should be subject to expedited reporting according to the same criteria as other ICSRs.. Careful medical evaluation should take place to decide on the need for further follow-up to ensure that the information is as complete as possible with regards to symptoms, treatments and outcomes.
Lines 622-627		*A suspected adverse reaction to an investigational medicinal product or non-investigational medicinal product occurring in a clinical trial which falls under the scope of Directive 2001/20/EC is only to be reported or followed-up based on the requirements detailed in that Directive. It is therefore excluded from the scope of this Module even if the clinical trial where the suspected adverse reaction occurred is 630 a post-authorisation safety or efficacy study, requested in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004, or conducted voluntarily.*

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: If the MAH becomes aware of SARs from investigator sponsored studies conducted with licensed product from MAH, this paragraph would indicate that the MAH has no submission responsibility, the sole submission responsibility lies with the sponsor. Proposed change (if any): If so, it would be helpful if the reporting responsibility sponsor vs. MAH could be stated more clearly.
Lines 766-767		Comment: The verbatim "possible" relies on causality assessment scales and as such might interfere with the meaning of implied causality for all assessment scales providing lower potential causalities between not related and possible (e.g. doubtful or unlikely) It should be clear whether "unlikely" would be assessed as reportable or not. Replace "reported " with expedited to be in line with the other sections of the GVP module. Proposed change (if any): Only reports of adverse reactions where a causal relationship with the suspected medicinal product is considered by the primary source or the marketing authorisation holder should be expedited;
Lines 938-940		GVP text: The marketing authorisation holder shall continue to collect any suspected adverse reactions related to the concerned medicinal product following the suspension of a marketing authorisation. The reporting requirements outlined in VI.C.4 remain. Comment: As outlined in line 947ff the above requirement serves to capture delayed onset adverse reactions. In the scenario where no marketing authorisation remains in the EEA but products with the same active substance continue to me marketed outside of Europe the reporting requirements with regards to non-EEA cases should be ceased. Otherwise expedited reporting of new onset third country cases will continue forever subsequent to commercial withdrawal from the EEA market.

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		Proposal: At the end of section VI.C.2.2.8. an additional sentence should be inserted as follows: If no marketing authorisation from the holder remains within the whole of the EEA, expedited reporting of third country case information can be terminated, while cases from EEA countries referring to the suspended EEA marketing authorisations will continue to be reported.
Line 957f		VI.C.2.2.10. Reports from class action lawsuits Comment: The inclusion in the guidance of an exemption to ICSR reporting in extenuating circumstances such as class action law suits is welcomed. However, the intended timeline of 30 days for *intial* expedited reporting is not in line with procedures in the USA under such circumstances (granting of waivers to report all cases within 60 days by the FDA). The opportunity to harmonise this should be taken now to avoid that cases created in the USA within 60 days may then be late cases under the EU legislation. Therefore, a timeline of 60 days should be allowed for, which appears fully justified because class action law suit cases will usually not provide new knowledge about the products safety profile. In addition, the GVP text should make clear that the exemption refers to both initial and follow up reports. Proposed changes for the GVP text: Where large batches of potential ICSRs are received, marketing authorisation holders may request, in exceptional circumstances, for an exemption in order to submit serious cases of suspected adverse reactions within 60 days from their date of receipt instead of 15 days. This proposition refers to both initial and follow up expedited reports.
Lines 987-992		Comment: The whole module does not lay down details for the requirements for the MAH to download ICSRs from Eudravigilance. In the lines 987-992 the overall principles of access provision are referenced, but this seems not enough information for such an important task, as once EudraVigilance is fully functional MAHs will no

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		longer receive copies of cases sent to CA in MS but will need to access those cases in EudraVigilance. Expectations on this process should be detailed here as well.
Lines 999-1003 vs. 1005-1007		Comment: CA in MS only need to provide the MAH with copies of serious cases, copies of non-serious cases would only need to be transferred to EudraVigilance. As non-serious cases need to be assessed in PSURs by MAH, it would seem reasonable for the CA in MS to provide copies of non serious cases to MAH as well.
Lines 1231-1233		*In accordance with [IM Annex I.3(4)(m)], a case narrative (data element ICH-E2B(R2) B.5.1) shall be provided, where possible, for all cases in accordance with the recommendations described in Chapter 5.2 of the ICH-E2D guideline*. Comment: The requirement to provide a narrative for all cases (serious and non-serious) does not fit with the implementing measures concept paper, Annex I 4 (m): *"(m) A case narrative providing all relevant information for individual cases where a serious adverse reaction(s) is/are reported by marketing authorisation holders. The information shall be presented in a logical time sequence, in the chronology of the patient's experience including clinical course, therapeutic measures, outcome and follow up information obtained. Any relevant autopsy or post-mortem findings shall also be summarised in the narrative. It shall be confirmed that no additional information is available."* In this document only narratives for serious cases are required. This should be harmonized, preferable to no narratives for non serious cases, Chapter 4.2. of E2D however does not limit a narrative to serious cases.
Lines 1238-1245		The narrative should serve as a comprehensive, stand-alone "medical report" containing all known relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical

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		course of the event(s), diagnosis, adverse reactions and their outcomes, relevant laboratory evidence (including normal ranges) and any other information that supports or refutes the suspected adverse reactions. Any relevant autopsy or post-mortem findings shall be summarised and related documents should be provided according to national regulation and if allowed by local data privacy laws. An example of a standard narrative template is available in the Report of the CIOMS Working Group V. Comment: It is common practice in industry that no or abbreviated case narratives in line with CIOMS V are written for non-serious expected safety reports to make efficient use of available resources and to focus on important safety information. The section about case narratives as proposed does not provide clarification whether the approach detailed in CIOMS V is still acceptable and it is desirable to have clarification on this. Proposed wording with one additional sentence: An example of a standard narrative template is available in the Report of the CIOMS Working Group V. In line with this, for non-serious expected safety reports the requirement to provide a stand alone full narrative does not apply.
Lines 1286-1289		Comment: Concerning the following two sentences: Significant new information relates to for example new suspected adverse reaction(s), a change in the causality assessment and any new or updated information on the case that impacts on its medical interpretation. Therefore, the identification of significant new information requiring expedited reporting always necessitates medical judgement. Proposed change (if any): Delete request of medical judgement regarding significant and insignificant change and require expedited reporting according to the described rules. Rationale: Lack of workload and costs as automatic transmission can be done by the system upon receipt of 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')*
Line 1293		Comment: Comment this is an example of unclear use of the "wording "expedited manner". Expedited can be both 15 or 90 day rule. Proposed change (if any): …considered as significant changes and thus reported in a 15 day expedited manner. For other examples a "90 days expedited manner" could be specified.
Chapter VI.C.6.2.2.7 – various lines		Comment: Examples of significant or non-significant changes are difficult to find in the module. Examples: Lines 1286-1289: **Significant** new information relates to for example new suspected adverse reaction(s), a change in the causality assessment and any new or updated information on the case that impacts on its medical interpretation. Therefore, the identification of significant new information requiring expedited reporting always… Lines 1302-1306: In contrast, a follow-up report which contains **non-significant** information does not require expedited reporting. This may refer, for example, to minor changes to some dates with no implication for the evaluation or transmission of the case, or corrections of typos in the previous case version. Naturally, medical judgment should be applied since a change to the birth date may constitute a **significant** modification (e.g. with implications on the age information of the patient). Lines 1307- 1307 Similarly, a change of the status of a MedDRA code/term from current to non-current, due to a version change of MedDRA, can be considered as a **non-significant** change as long as this change has no impact on the medical content of a case. However, an amendment of the MedDRA coding due to a change in the interpretation of a previously reported suspected adverse reaction may constitute a **significant** change and therefore should be reported in an expedited manner. Lines 569-575: When additional **significant** information is received for a previously reported case, the reporting time clock starts again for the submission of the follow-up report from the day of receipt of relevant

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')*
		follow up information. For the purpose of reporting, **significant** follow-up information corresponds to new medical or administrative information that could impact on the assessment or management of the case or could change its seriousness criteria; **non-significant** information includes updated comments on cases assessment or corrections of typographical errors in the previous case version. See also VI.C.6.2.2.7 as regards the distinction between significant and non-significant follow-up information. Proposed change (if any): 1. Replace title VI.C.6.2.2.7. Follow-up information by VI.C.6.2.2.7. Significant and non significant follow-up information 2. Define non significant and significant in GVP module annex (definitions).
Lines 1450-1454		GVP text: Where an adverse reaction(s) report is associated with a quality defect of a medicinal product, the MedDRA Lower Level Term code 10069327, corresponding to the term "Product quality issue", should be added to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1.b). Comment: In line with the recommendations of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider' we suggest to code the reported quality defect as close as possible to the reported verbatim to allow an accurate analysis of such reports. For example, a patch adhesion issue should be coded to "medicinal patch adhesion issue (LLT term code 10069938)" and not to the less specific term "product quality issue". The latter should only be used if no accurate LLT term is available. An appropriate search strategy still allows to retrieve all product quality issues as appropriate. Proposed wording: Where an adverse reaction(s) report is associated with a quality defect of a medicinal product, the MedDRA Lowest Level Term closest to the reported verbatim should be selected to code for the quality defect. If no matching Lowest Level Term is available the code 10069327, corresponding to the term "Product quality

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')*
		issue", should be added to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1.b).
Lines 1723-1730		GVP text: Articles can be excluded from reporting by the marketing authorisation holder if another company's branded medicinal product is the suspected medicinal product. In the absence of a specified medicinal product source and/or invented name, ownership of the medicinal product should be assumed for articles about an active substance. Alternative reasons for exclusion of a published article are a specified formulation or a route of administration that is not consistent with the marketing authorisation holder's medicinal product presentation. The caveat is that articles may describe the preparation of an extemporaneous product (for example making solutions from solid dose forms), and could, therefore, be reportable. Comment: The exclusion criteria for articles from the literature provided in lines 1723 to 1730 should be consistent with the exclusion criteria as provided in line 829 to 832 which reads as follows: *Where ownership of the medicinal product by the marketing authorisation holder can be excluded on the basis of the active substance name, formulation, route of administration, primary source country or country of origin of the suspected adverse reaction, the ICSR should not be reported to the competent authorities in Member States, or to the EudraVigilance database* Proposal: The text in line 1723ff exclusively mentions another company's branded medicinal product as reason for exclusion. Behind this first sentence, the following should be added to reflect the identical conditions as outlined in line 829 ff: Articles can be excluded from reporting by the marketing authorisation holder if another company's branded medicinal product is the suspected medicinal product. Alternative reasons for exclusion of a published article are when either of the following not consistent with the marketing authorisation holder's medicinal product

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')*
		presentation: the active substance name, formulation, route of administration, primary source country or country of origin of the suspected adverse reaction, the primary source country, the country of origin of the suspected adverse reaction.
Lines 1771-1774		Comment: Copy right is not respected Example: 1. Mailing address and format of literature articles: Literature articles reportable to the Agency should be provided in PDF format and sent via e-mail to the following e-mail address: EVLIT@ema.europa.eu. Literature articles reportable to the competent authorities in Member States should be provided in PDF format and sent according to the local requirements. Proposed change (if any): Literature articles should be provided by the source in Vancouver style.

Please add more rows if needed.

<Date of submission>

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

Comments from:

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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (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')*
293		Comment: The following instruction is ambiguous: this also applies to reports identified in the scientific and medical literature that originate in a country where a company holds a marketing authorisation but has never commercialised the medicinal product. Proposed change (if any): reports identified in the scientific and medical literature that originate in a country where a company holds a marketing authorisation but has never commercialised the medicinal product can be disregarded for ICSR collection purposes.
349		Comment: The four criteria for case validation are in this section confused with criteria for expedited reporting. This section should be rephrased to explain what a valid case is. The criteria for expedited reporting should be discussed in a different section. Proposed change (if any): Rephrasing: At least one suspected adverse event (see VI.A.2.1). If the primary source has made an explicit statement that a causal relationship between the medicinal product and the adverse event has been excluded and the recipient (competent authority or marketing authorisation holder) agrees with this, the report qualifies as a valid adverse event report. The report can be considered as incomplete if it is reported that the patient experienced an adverse reaction and there is no information provided on the type of adverse reaction experienced.

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		Contradiction with line 349 on "valid ICSR": should not be reported on an expedited manner since there is no suspected adverse reaction. These reports should however still be processed as ICSRs in the safety database. Proposed change: adapt definition valid ICSR in line 349.
557		Incomplete description what should be reported expeditedly: **Only valid ICSRs (see VI.B.2) should be reported.** This statement is incomplete because it is obvious from preceding chapters that not all valid ICSRs apply for expedited reporting. This chapter does not provide any information on which ICSRs should be reported in an expedited manner. Proposed change: add reference to table in appendix, line 1872.
585		The following statement provides no information on the time-frame for reporting of non-serious cases, nor has this been mentioned in the preceding chapters: the reporting time frame for non-serious reports should then be applied for the subsequent follow-up reports. Propose change: add reference to table in appendix, line 1872.
1824		**If the case has been received from a National Competent Authority (NCA), do not retransmit it to another NCA nor to EudraVigilance (EV).** This is in conflict with the MHRA Black Triangle requirement. Proposed change: additional text "unless specifically demanded by a NCA".

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 18, 2012

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

Comments from:

Name of organisation or individual
[redacted], WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre)

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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	This guideline is a series of documents providing comprehensive guidance on good pharmacovigilance practices in the regulatory context. As such, they will undoubtedly serve an important purpose in clarifying new Directives and Regulations applicable in the EU in this area. Providing the operative framework for competent authorities in EU Member States, marketing authorisation holders and the EMA, these guidelines will also be seen as setting the standard for what will be regarded as compliance with existing rules and regulations. The Scope statement in the Introduction states "All applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb "shall". Guidance for the implementation of legal requirements is provided using the modal verb "should"." It would be helpful if the whole section "Referencing of legal requirements in GVP" from the GVP Introductory Cover Note was included in every document, to help the understanding of the paragraph above. Having read the instructions, my interpretation of the use of "shall" and "should" is that a "shall", together with a clearly stated reference to applicable Directive or Regulation refers to a legally binding requirement. Can one assume that a "shall" without reference to the legislation or the IM means that the requirement is a recommendation and not legally binding? Some examples of where there could be interpretation issues are found on lines 732, 944, 1248, 1352, 1357. Each business rule and SOP cost money and takes time and effort to develop and adhere to; that is why it is so important that the distinction between *legally binding* requirements and *recommendations* is crystal clear. ***VI.C.5. Collaboration with the World Health Organization and the European Monitoring Centre for Drugs and Drug Addiction*** The WHO Collaborating Centre for International Drug Monitoring (also referred to as Uppsala Monitoring Centre), WHO-UMC, is responsible for the scientific and technical operations of the WHO International Drug Monitoring Programme, and is the body referred to on l. 1045. To avoid any risk of possible misunderstandings (there are more than 800 WHO Collaborating Centres around the world), it is recommended to spell the name in full. The statement on l. 1047-1049 "It will replace the requirements of Member States participating in the WHO Programme for

Stakeholder number *(To be completed by the Agency)*	General comment
	International Drug Monitoring to directly report to WHO suspected adverse reactions (sic) reports occurring in their territory." is surprising. All EU Member States are also members of the WHO International Drug Monitoring Programme, ratified by the World Health Assembly. This membership is based on bilateral agreements between governments in each country and the WHO, in which each country has committed to submit their data to VigiBase, the WHO Global Individual Case Safety Report Database, managed by the WHO Collaborating Centre for International Drug Monitoring. These agreements are completely separate from the EU legislation requiring EMA to make available all reports occurring in the EU to WHO-UMC. It would seem like a good idea for Member States to only have to submit their data once – for that reason we at WHO-UMC have an ongoing dialogue with EMA on how this could be implemented. Also, we are naturally interested in receiving reports from MAHs, which from now on will not be sent to the individual Member States, but directly to EMA. We look forward to continued discussions and to try to find good practical solutions for data transfer from EMA to WHO-UMC/VigiBase. However, EMA transferring reports from the individual countries to WHO-UMC is a practical solution that in my mind does not per se supersede countries' agreements with WHO. As I understand it, it is a decision between Member States and WHO how the reporting requirements for members of the WHO Programme for International Drug Monitoring are fulfilled. A clarification of the meaning of the statement on l. 1047-1049 is requested. ***VI.C.6.2.2.8 What to take into account for data privacy laws*** This is an important and interesting section. The issues around data protection have been an integral part of the discussions between WHO-UMC and EMA referred to above. EMA representatives have stated that WHO-UMC cannot receive all data fields in ICSRs sent to EMA, and that the data sent by EMA to WHO-UMC/VigiBase will contain the data fields specified in Annex I to the EudraVigilance access policy for medicines for human use, EMA/759287/2009 corr. According to l. 1333-1334 "the processing of personal data within the EudraVigilance database is possible while respecting EU legislation in relation to data protection".

Stakeholder number *(To be completed by the Agency)*	General comment
	Just as the EMA, WHO-UMC requests members of the WHO International Drug Monitoring Programme to provide data in form of Individual Case Safety Reports as defined by ICH E2B guidelines, and European countries have been providing ICSR data to the WHO-UMC for 40 years without problem. Similar texts are included in ICH E2B as pointed out in the GVP Module VI document, "Where in accordance with applicable national legislation, information related to personal data cannot be transferred to the EudraVigilance system, pseudonymisation may be applied" - thus this applies also to data sent to WHO-UMC/VigiBase. It should be pointed out that WHO-UMC is a Swedish foundation, the purpose of which is to do pharmacovigilance for the world, including EU, as defined by WHO as "The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems." The very same definition has been taken for use by EMA (included in GVP Annex I). WHO-UMC cannot fulfil its international mission if it receives data that does not allow for a clinical medical assessment. A clarification is requested as to why the data fields included ICH E2B reports can be processed in EudraVigilance, but not in VigiBase.

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):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

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

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We generally agree with the provisions described in this 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')*
Lines 293 - 295		Comment: We do not agree with this policy when it comes to reports related to active substances authorised to more than one marketing authorisation holder (MAH) in a specific country (e.g. generics), as this will only result into duplicate reports being reported in EudraVigilance. We propose that in those cases, only MAHs who market (or have marketed in the past) a specific product shall report the relevant cases, unless there is reason to believe that the product has been imported by another country i.e. though compassionate use programs. Proposed change (if any): This also applies to reports identified in the scientific and medical literature that originate in a country where a company holds a marketing authorisation but has never commercialised the medicinal product, unless the marketing authorisation holder can ascertain that their product has never been imported in this country through any legal means.