4 September 2014
EMA/540396/2014

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

GVP Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1) (EMA/873138/2011)

The draft of this module was released for public consultation between 7 June and 5 August 2013. The module has been revised, taking the comments received into account.

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

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

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

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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' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
Union Européenne des Médecins Spécialistes European Union of Medical Specialists (UEMS-D/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	Outcome *(To be completed by the Agency)*

No comments – well done

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)*
		Comment: no Proposed change (if any):	
		Comment: no Proposed change (if any):	
		Comment: no Proposed change (if any):	

Please add more rows if needed.

2013.06.21

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (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	Outcome *(To be completed by the Agency)*

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)*
Lines 608-610		Comment: Please consider redefining of the day 0. The receiver may obtain AR report *e.g.* via e-mail ("be informed") on one day but read it on the next day ("be aware"). Proposed change: It is the first day when a receiver is ~~informed~~ aware of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday.	

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' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
Research Quality Association

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1. General comments

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

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)*
604 - 610		Comment: In reference to VI.B.7, the removal of the text that provides context to this clock start will have a significant impact on the procedural and contractual obligations of many MAHs. MAHs have been subject to regulatory inspection where the definition of day 0 starts with awareness (e.g. when the information is triaged during a working day) and not with the date of being informed by the reporter. I would question whether it is practical to expect an MAH to be aware of (i.e. gain knowledge) of the event during office closure. The MAH does not function on a 24/7 365 basis with regards to triage of case information. Furthermore, wording between Directive 2010/84/EU Article 107 (and Vol 9a referred to in Regulations (EC) 726/2004 and (EU) 1235/2010) now appears inconsistent with section VI.B.7. No explanation for this deletion is provided in the clarification text within revision 1. Proposed change (if any): Provide rationale for clarification/change	
779 - 797		Comment: The amended text indicates that only those adverse events identified in the protocol as being actively sought are subject to reporting. This indicates that if an adverse event (where the outcome is not fatal) suspected to be related to the studied medicinal product is collected, it wil	

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		not be subject to expedited reporting as part of the non-interventional study, and will be summarised in the interim or final study report. Proposed change (if any): Reference should be made that those adverse events not actively sought but suspected to be related to the studied medicinal product should nonetheless be reported to the Sponsor/MAH to ensure complete safety data collection, assessment, and reporting.	
766 - 773		Comment: The definition of Sponsor for post-authorisation studies has been clarified and extended to make the support and influence of the MAH more sensitive. Proposed change (if any): It is suggested that this change is clarified and put in to context, such that it applies only to post-authorisation studies initiated after this revision is finalised and released.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 August 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
Pfizer Inc

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Overall, this proposal to revise module (GVP Module VI – Management and reporting of adverse reactions to medicinal products, rev. 1) is very helpful and provides additional detailed guidance on the collection, data management, and reporting of suspected adverse reactions associated with medicinal products authorised for human use in the EU. We recognise the efforts of the Agency to improve the already comprehensive guidance. Further, we appreciate the opportunity to review the revised document and provide the following comments with the goal of improving and strengthening the revised guidance prior to it becoming effective.	
	While, overall, the proposed revision provides useful updates, it does not clarify certain very important points in the following sections: VI.B.2. Validation of reports To be consistent with CIOMS V consensus recommendations, a reporter's first-hand knowledge of a patient should qualify as an identifiable patient in the absence of other identifiers. VI.C.2.2.11. Reports from patient support programmes and market research programmes Safety reports originating from these programmes should only be considered solicited when they are the focus of the study and are actively sought. VI.C.6.2.3.7. Reports originating from organised data collection systems and other systems	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The logic of this section should be reviewed to ensure that expectations are clear. Specific comments on these sections are provided below, as well as additional comments that address the changes introduced in the proposed revision to the module. Proposed changes are highlighted with **<u>bold underlined</u>** text.	

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)*
204-206		Comment: The initial sentence focuses on the SmPC particulars, but, in contrast to the next sentence, seems to give little room for clinical judgement. The latter sentence could be strengthened with examples. Proposed change: Revise wording on line 206: "Clinical judgement should always be applied**, considering, for example, the medicinal product's specific profile, its expected therapeutic index, patient characteristics, severity of disease, or treatment indication, etc.**" provide interpretation to "clinical judgement vis-a-vis initial sentence: should each drug's specific profile (i.e., therapeutic index) be factored in? Or subject's characteristics? Or treatment indication?	
396-397, 413-414		Comment: For a valid report (and in keeping with data privacy laws), the module states the requirement for "one single identifiable patient characterised by initials, patient identification number, date of birth, age, age group or gender." Further, "The lack of any of these four elements means that the case is considered incomplete and does not qualify for reporting." This is not consistent with the consensus recommendations in the CIOMS V report, which indicates that a reporter's first-hand knowledge of the existence of a patient makes the patient identifiable. The rationale behind the CIOMS recommendations is that criteria for patient identifiability should not be so stringent as to exclude reports that could be medically important. However, vigilance must be maintained to prevent duplicate reports of the same suspected reaction. The CIOMS report clearly indicates that, in the absence of criteria identifying criteria listed above, e.g., patient details, a	

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		case should be considered valid (with respect to an identifiable patient) as long as there is first hand-knowledge of the patient. Proposed change: Revise line 397: "...age, age group or gender. **<u>In the absence of all of these characteristics, a reporter's first-hand knowledge of the existence of a unique patient qualifies the patient as identifiable.</u>** The information should be ..."	
731-736		Comment: The PASS description on lines 731-736 is not consistent with that given in Directive 2001/83 (as amended) and in GVP Annex I (rev 1). The module states that a PASS could be *an activity other than a non-interventional study*, including a patient survey or information-gathering on efficacy or patient compliance (italics added for emphasis): "In the context of this module, post-authorisation studies are organised data collection systems which do not fall under the scope of the clinical trials Directive 2001/20/EC. "They include non-interventional post-authorisation studies, <u>compassionate use, named patient use, other patient support and disease management programmes, registries, surveys of patients or healthcare providers, and information gathering on efficacy or patient compliance</u>. ~~They may involve the receipt of information on adverse events.~~" This is not consistent with GVP Annex I (rev 1) definition of a PASS (p 14), which is taken from the definition of a PASS in Directive 2001/83 (as amended): "Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		measuring the effectiveness of risk management measures." The activities underlined above would not normally be understood to amount to a "study". Proposed change: Revise wording on lines 733-736: "~~**They include non-interventional post-authorisation studies, compassionate use, named patient use, other patient support and disease management programmes, registries, surveys of patients or healthcare providers, and information gathering on efficacy or patient compliance.**~~ ~~They may involve the receipt of information on adverse events.~~" **A PASS is any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures~~.~~ (Directive 2001/83/EC, as amended)**."	
766-773		Comment: The module defines when an entity will be considered the "sponsor" of a PASS and therefore responsible for case reporting arising from the PASS. It is not entirely clear whether the text on line 769 ("... financed, initiated, managed ... ") is meant to mean "... financed **or** initiated **or** managed …" or "... financed **and** initiated **and** managed…." In addition, there are many different types of arrangements where MAHs and non-commercial organisations cooperate to conduct research studies. It would be helpful to have further guidance on case reporting obligations in hybrid situations. For example, it is not uncommon for an MAH to supply study drug together with partial financial or in-kind support for a study conducted in an academic setting. What is the expectation regarding designation of sponsorship in such an example,	

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		assuming that the MAH does not influence the protocol, manage the study, or monitor the clinical data, etc.? Also, what is the expectation regarding sponsorship and reporting obligations where a PASS is financed/initiated by more than one MAH, e.g., as sometimes happens for IIRs within the oncology field? Would each MAH be deemed to be the "sponsor" in relation to the AEs for their product? How would this work in practise? Proposed change: Revise wording on line 768: "However, where a study **involves a single marketing authorisation holder and** is directly financed **(fully) or** initiated **or** managed (fully or partially) or where ~~the~~ its design is influenced by **~~a~~ the** marketing authorisation holder …" and Supplement wording on line 773: "... Module. **However, when a single marketing authorisation holder or multiple marketing authorisation holders provide study drug(s) together with only partial financial or in-kind support to an academic investigator, the study would be considered under academic sponsorship and the reporting obligations detailed in this module would be the responsibility of the academic sponsor**."	
779-797		Comment: It would be helpful to have additional guidance on expectations regarding criteria for the events (serious or non-serious) to be actively sought or not actively sought, e.g., should listed or identified events be excluded, etc.? Proposed change: Revise line 788: "... (such as in a drug utilisation study). **In addition, it may be appropriate to exclude events that**	

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		have already been well-characterised, i.e., identified and listed in the company core data sheet/SmPC. For adverse events actively sought ..."	
792-795		Comment: Case reporting should focus on events that are actively being sought and where causality has been established. All other serious and non-serious reports of adverse events, which are not actively sought according to the protocol, should only be summarised in the interim or final study report; they should not be reported as ISCRs to the competent authorities. Proposed change: Revise line 792: "All **unrelated serious and non-serious reports, as well as all ~~other~~** serious and non-serious reports of adverse events, **that** **~~which~~** are not actively sought according to the protocol, should only be summarised in the interim or final study report; they should not be reported as **ICSRs** **~~ISCRs~~** to the competent authorities."	
1091-1095		Comment: If an AE is received, but it is not actively sought, then it would logically be more appropriate to consider it as a spontaneous report, e.g., spontaneous (stimulated) report, rather than a solicited report. Categorisation of a report as solicited should be applied only when adverse event information is actively sought, as clearly indicated in other sections of this module. In contrast, this section of the module is contradictory in suggesting that all organised data collection schemes, including all patient support and marketing programs, are to be handled as solicited reports, with no exceptions. Also, see comment regarding lines 1656-1661. There is a further opportunity to provide the definitions of a patient support programme and a market research	

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		programme in GVP Annex I. Proposed changes: (a) Revise line 1091: "Safety reports originating from those programmes **in which safety information is actively sought** should be considered as solicited reports. **Safety reports from programmes that do not actively seek safety information should be considered spontaneous reports and processed accordingly.** Marketing authorisation holders should have the **~~same~~ appropriate** mechanisms in place **~~as for all other solicited reports~~** (see VI.C.2.2.2.) to manage ... " (b) Revise line 1095: Valid ICSRs should be reported **~~as solicited~~** in accordance with the electronic requirements provided in VI.C.6.2.3.7.**~~:~~** (c) Provide the definitions of a patient support programme and a market research programme in GVP Annex I.	
1656-1661		Comment: Adverse events are not actively sought in all patient support programs or market research programs. In the absence of active solicitation, adverse events reported from such programs are spontaneous and should not be classified as solicited. Proposed change: Revise line 1656: "1. **Where adverse events are actively sought from ~~For all~~** patient support programmes **or~~,~~** market research programme**s or~~,~~** non-interventional studies with primary data collection from consumers and healthcare professionals **or~~, and~~** for certain compassionate use or named patient use **programmes:** ~~where adverse events are actively sought"~~	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
1678-1685		Comment: This wording does not seem to be consistent with generally accepted consensus recommendations: "3. For clinical trial conducted in accordance with Directive 2001/20/EC and where the adverse reaction is only suspected to be related to a non-investigational medicinal product (or another medicinal product which is not subject to the scope of the clinical trial) and there is no interaction with the investigational medicinal product: "• the report should be considered as spontaneous report; as such it conveys the suspicion of the primary source;" Since these reports originate from organized data collection schemes, they would be considered as solicited according to ICH guidance and CIOMS recommendations, as well as by all other regulatory agencies. In instances when a marketing authorization holder does not conduct the programme directly, it is customary for the marketing authorization holder to execute a written contract and protocol indicating that all SAEs and AEs are to be forwarded to the company. Consistent with the principles of good clinical practice, all such events are also collected in a clinical database and processed as solicited events. In addition, in a clinical trial setting, there is no specific guidance for handling an ADR that is considered related to both the IMP and a concomitant medication and is assessed as expected (per the single safety reference document for the IMP). Thus, in this scenario, the event, even if related to the IMP, will not be reported to the EVCT module. No guidance is provided that would require creation of a spontaneous report for the concomitant suspect; therefore, such a case report would not be submitted to EudraVigilance. Proposed change: Revise line 1678: "3. For clinical trial**s** conducted in	

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		accordance with Directive 2001/20/EC and where the adverse reaction is only suspected to be related to a non-investigational medicinal product (or another medicinal product which is not subject to the scope of the clinical trial) and there is no interaction with the investigational medicinal product: "• the report should be considered as ~~**spontaneous**~~ **a** report **from an organised data collection system and such reports should be processed as solicited reports**; ~~**as such it conveys the suspicion of the primary source;**~~"	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 July 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
Novartis Pharma AG Novartis Vaccines & Diagnostics Novartis Consumer Health

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Novartis welcomes the proposed revisions to GVP Module VI, in particular the clarification of requirements for data collection from non-interventional studies. Other revisions, such as the definition of Day 0, and the removal of repetition (removal of references to 'patient' where this is included in the definition of 'consumer') are appreciated, as they further improve the module.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
198, 262, 571, 608, 671 & 735		Comment: Agree with the change, this is consistent with the definition provided in GVP Annex 1 and removes the tautology (patient is included in the term 'consumer', by definition). No proposed change.	
735 & 736 739 739		Comment: Agree with the deletion of text. It would be helpful to insert cross-references to the following two sections at this point: ***VI.C.2.2.2. Solicited reports*** ***VI.C.6.2.3.7. Reports originating from organised data collection systems and other systems*** Proposed change: Add cross-reference to ***VI.C.2.2.2. Solicited reports*** ***VI.C.6.2.3.7. Reports originating from organised data collection systems and other systems*** after the reference to post-authorisation studies in line 739.	
775 to 797 (inclusive)		Comment: This text is complex and the structure is difficult to follow, leading to the potential for misinterpretation. The proposed change as below sets out the text in a tabular format, which aids interpretation and captures the intended meaning more clearly. Proposed change (if any): See table overleaf.	

VI.C.1.2.1. Non-interventional studies

Requirements for non-interventional studies with primary data collection direct from healthcare professionals or consumers.

Table [No]. Collection and Reporting requirements for Non-interventional studies

Type of event	Collection requirement	Reporting requirements
Actively sought for inclusion as per the study protocol	Collect HCP and consumer reports and add to both study and safety database as ICSR	Expedited reporting (as solicited reports) of valid ICSRs (see VI.B.2 adverse reactions suspected to be related to the studied medicinal product)*
Actively excluded as per protocol (including death or fatal outcomes AEs)**	Collect as specified in the protocol and retain in the study database only	Do not report as ICSRs Summarise in the interim or final clinical study report
All other AEs reported but not actively sought in the protocol	Collect HCP and consumer reports and retain in the study database only	Do not report as ICSRs Summarise in the interim or final clinical study report

* For electronic reporting of ICSRs, the recommendations provided in VI.C.6.2.3.7 should be followed.

** Justification for this exemption should always be provided for example:

- They represent outcomes of the study (efficacy end point)
- Patients included in the study have a disease with high mortality
- Occurrence of death has no relation to the objective of the study (such as in a drug utilisation study)

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
768 to 773		Comment: Revised wording is clear and helpful. No proposed change.	
1523 to 1525		Comment: We do not agree to this proposed change. The footnote may cause technical issues due to the use of special characters and non-English keyboards. Both of these items are outside of the harmonised ICH E2B format, and may lead to failures of electronic data interchange. Use of verbatim text from the original report may cause misunderstandings outside of the EEA, and does not add any value to the ICSR. Proposed change (if any): Request to strike through the new text on line 1523 and to delete the accompanying footnote [38] plus the citation in line 1525.	
2047-2048		Comment: The URL specified within the draft Revision 1 text is incorrect. This must be replaced with the correct hyperlink (Revision 6 document was published on 15 Jul 2013, Revision 7 on 25 Jul 2013). Proposed change (if any): URL for EMA/321386/2012 Rev. 7 is now @ http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127657.pdf	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 August 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
Mundipharma Research GmbH & Ko.CG

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1. General comments

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

Mundipharma welcomes this update to Module VI and the possibility to comment. Particularly the proposals to address the important area of data collection from non-interventional studies are helpful. We have exclusively provided comments about this issue.

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)*
789-797	15	Comment: The meaning of "active seeking" has not been determined anywhere in the legislation. Mundipharma interprets this to mean that once an AE form mandating the capture of every AE is being used as integral part of a non-interventional study, this procedure alone fulfils the definition of "active seeking" of AEs. The alternative interpretation would have been that "active seeking" indicates the insertion of one or multiple particular AE terms into the AE form with the goal to solicit these particular terms and learn more e.g. about their frequency, severity and/or outcome (example: constipation of in an opioid study). Based on the latter interpretation the way the text in GVP VI Rev 1 reads would indicate that all valid cases of constipation qualify for reporting, whilst all other AEs that are not specifically solicited within the AE form would not qualify for reporting. In the given example of constipation under opioids reporting procedures would not appear sensible or reflecting the interest of patient safety; this is because every occurrence of an acknowledged ADR would be reported just because it is being "actively sought" within the AE form - opposed to not reporting all other ADRs including potentially unlisted rare ADRs which will be captured in the AE form without being solicited therein. According to the above Mundipharma is convinced 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')*	Outcome *(To be completed by the Agency)*
		initially mentioned interpretation of "active seeking" (use of a standard AE form mandating the capture of every AE that had occurred in the study population) reflects a proper definition of active seeking. A clarifying statement may be added to the text in the module that might e.g. read as follows: "Active seeking" in the context of this module means use of a standard AE form mandating the capture of every AE that had occurred in the study population, but does not refer to soliciting of particular AE term(s) specifically. In addition, based on this understanding the text should be rephrased to indicate that the protocol will define whether specific AE terms might be exempted from ICSR reporting and thus only be summarised in the interim or final study report (in the given example constipation), whilst all other reported ADR terms would qualify for AE reporting [The constipation example may be replaced by any other example as traditionally used in the setting of interventional clinical trials where e.g. SAEs representing trial endpoints which will be fully analysed as primary or secondary endpoints in the study report are exempted from ICSR reporting]. Mundipharma also feel that the term "sponsor" which has a defined meaning in the setting of interventional clinical trials should not be used in Module VI at all to avoid confusion between the different sets of regulations aiming at interventional trials versus postmarketing safety reporting, particularly as the sponsor has particular obligations under	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		DIR 2001/20 EC which a "sponsor" of a non-interventional study would not have. Acceptance of this comment may call for a final check of the Module VI to make amendments as suggested in the below proposed text Lastly (as a minor comment) we considered whether the text "serious and non-serious" adds value; we feel a slight tendency in favour of its deletion to make the sentence shorter. Proposed change (if any): ~~***For adverse events actively sought according to the protocol,***~~ ***O****nly valid ICSRs (see VI.B.2.) of adverse reactions suspected to be related to the studied medicinal product should be reported* ***from company sponsored studies*** *(as solicited reports) by the* ~~***sponsor***~~ ***marketing authorisation holder*** *to the competent authorities. With regards to the electronic reporting of ICSRs, the recommendations provided in VI.C.6.2.3.7. should be followed. All other* ~~***serious and non-serious***~~ *reports of adverse events*~~***, which are not actively sought according to the protocol,***~~ *should only be summarised in the interim or final study report* ***as determined by the protocol of the study****; they should not be reported as ISCRs to the competent authorities.*	
		Comment: Proposed change (if any):	
		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')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 August 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
CBG-MEB (Medicines Evaluation Board – The Netherlands)

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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)*
	A general comment concerns the term ‘sponsor’, which is used in the context of academic research in this GVP. Even 9 years after the Clinical Trial Directive entered into force the term ‘sponsor’ still causes a lot of confusion. It is often wrongly interpreted as the organisation who has given a financial contribution. GVP VI now refers to 'academic sponsor' and also states that the study can be financed, managed, initiated by MAHs. This might be confusing and we suggest to avoid the term 'sponsor' here and to rephrase to ‘academic research’ where appropriate.	

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)*
731-736		Comment: Patient support programmes have been categorised as a post-authorisation study. It could be considered that patient support programmes involve a range of activities, not necessarily designed to be organised data collection schemes. Although the information may be relevant from a safety point of view, it would not necessarily be suitable for ADR reporting. Proposed change (if any): Please consider that relevant safety information arising from PSP programmes could be communicated to Regulatory Authorities via other means than ICSR reporting.	
766-797		Comment: Some NCAs perform intensive monitoring studies in which patients/HCPs are requested to report any event. It is not very clear which reporting rules would apply to these studies. Is the following understanding correct: for intensive monitoring studies conducted by NCAs, if the protocol does not specify which events are collected, it is OK to summarise events in the interim or final study report only and there is no need to do a causality assessment for each event reported and there is no need to report to EudraVigilance. Proposed change (if any):	
1666		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')*	Outcome *(To be completed by the Agency)*
		With these conventions for data entry it will not be possible to distinguish reports from Patient Support Programmes (PSP) from other reports. Nowadays, NCAs receive many cases from PSPs flagged as spontaneous reports, most poorly documented and reporting hardly anything else than 'death'. This is not very useful for signal detection purposes. Furthermore, with the ADR databases being publicly accessible, this is raising a lot of questions and concerns from the general public. Proposed change (if any): In general, reports from organised data collections systems should not be flagged as spontaneous reports. Situations in which 'true' spontaneous reports arise from an organised data collection could perhaps be clarified, and it should be stated that this is an exception. Also, it is suggested to make cross-reference to lines 405-407, where it is stated that the report is not valid if only an outcome (or consequence) is notified and no further information is provided about the clinical circumstances to consider it as a suspected adverse reaction.	
		Whereas out of scope of this public consultation, please allow us to address the following situation, as the GVP seems to provide contradicting guidance: A NCA has sent an initial report to the MAH, and the MAH receives additional information from a HCP/consumer. The initial report is considered as a 'regulatory report' and as such	

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		will not be submitted by the MAH. How should the MAH handle the follow-up information? GVP Module VI reflects that E2B allows for re-transmission of case: "During this re-transmission process, information on the case should not in principle be omitted or changed if no new information on the case is available to the re-transmitting sender. (section VI.C.6.2.5. Electronic re-transmission of ICSRs between multiple senders and receivers)" This could be interpreted in a way that the MAH is allowed to update the NCA case with the follow-up information received. Current guidance in GVP Module VI also states that: "When one party (competent authority or a marketing authorisation holder) is made aware that the primary source may also have reported the suspected adverse reaction to another concerned party, the report should still be considered as a valid ICSR. All the relevant information necessary for the detection of the duplicate case should be included in the ICSR". In practice this could be interpreted in a way that the MAH would need to create a new case (with a new worldwide case identification number), that refers to the NCA case (via the duplicate section). However, this approach would also mean that both the MAH database, as well as the NCA database and the EMA EudraVigilance database would have to deal with the duplicate reports.	

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' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
LEEM working group on Non Interventional Study

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1. General comments

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

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)*
Lines 779 to 781		Comment: We propose to add "and any safety objectives" (line 780) as the possibility should remain for a sponsor to perform a study without AE collection if the study has no safety objectives at the condition that HCP are reminded to report as for marketed products outside a study (see proposal to be added after line 797). The terms "any AE" needs clarification: Could you confirm that "*any AE to be actively sought*" should be read as : Any AE medical entities such as QT prolongation, hypoglycemia… Could you confirm that AE should not be considered as actively sought when asking for general safety such as "has the patient presented any AE" ? Proposed change (if any): For ~~N~~non-interventional studies with primary data collection directly from healthcare professionals or consumers, **and any safety objectives**, non-academic sponsors should specify in the protocol ~~any~~ **all** adverse events (serious or non-serious) to be actively sought	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		Proposal to add the following paragraph after line 797: **For non-interventional studies with primary data collection directly from healthcare professionals or consumers, and no safety objectives, the reporting by HCPs and sponsors of ICSRs potentially occurring should follow the recommendations provided for spontaneous notification outside a study.**	
Lines 792 to 795		Comment: We are of the opinion that serious suspected adverse reactions (even those not actively sought) should be reported by the sponsor to the CAs. Proposed change (if any): **For other adverse events not actively sought according to the protocol, only valid ICSRs (see VI.B.2.) of Serious adverse reactions suspected to be related to the studied medicinal product should be reported (as solicited reports) by the sponsor to the competent authorities. Other reports of adverse events (not suspected serious AE and non-serious AE whatever the suspectedness is), which are not actively sought according to the protocol, should only be summarised in the interim or final study report**	
Lines 799 to 800		Comment: We understand that there is no need to collect these adverse events serious and non-serious in the safety	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		database. Proposed change (if any): **If the study has safety objectives,** ~~R~~reports of adverse events/reactions should only be summarised in the interim or final study report~~, where applicable~~.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 August 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
Italian Society for Applied Pharmacological Sciences - Pharmacovigilance Working Group

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1. General comments

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

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)*
608-610		Comment: it might be more explicatory to indicate first 24 hrs after receival of the information of a valid ICSR , instead of first day. Proposed change (if any):	
735-736 738-739 766 769-772		Comment: the new description is more than sufficiently exhaustive and does not require further clarification. Proposed change (if any):	
1656		Comment: no clarifications requested. Proposed change (if any):	
2045-2057		Comment: not understood the requests. Proposed change (if any):	
198		Comment: the PATIENTS wording should not be cancelled, since it is saved the eventual reporter's opinion. 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')*	Outcome *(To be completed by the Agency)*
262		Comment: the wording with OR makes things more evident. Proposed change (if any):	
571		Comment: the PATIENT wording should be cancelled, since reports are NOT reported as ICSRs. Should a follow-up ensure the information, the narrative might include also patient's opinion, if required. Proposed change (if any):	
671		Comment: no idea! But if Member States are required, it should be indicated also in Figure VI. Proposed change (if any):	
914		Comment: MAH certainly have a PV system in place, therefore the words "post authorisation studies" might be deleted. Proposed change (if any):	
1523 1525		Comment: the eventual requirements (by international or local authorities) being the prerequisites, it might be stated that an English translation is always requested as an accompanying document. CIOMS forms might be used for this purpose. 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')*	Outcome *(To be completed by the Agency)*

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 July 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
Irish Medicines Board

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1. General comments

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

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)*
607-610		Comment: Proposed change (if any): This date should be considered as day zero **and** ~~**it**~~ is the first day when a receiver is informed of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday. ~~In practice this is the first business day the receiver becomes aware of the information.~~	
737-741		Comment: Proposed change (if any): Competent authorities in Member States and marketing authorisation holders should have in place a system to collect full and comprehensive case information on adverse events that are **identified from these data collection systems** ~~**actively sought in post authorisation studies**~~ and to evaluate that information in order to determine whether the collected adverse events are possibly related to the studied (or supplied) medicinal product and should be classified and processed as ICSRs of suspected adverse reactions.	
		Comment: Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 August 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
INFARMED

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	As most of Member States don´t have local requirements regarding the reporting of cases of suspected adverse reactions from academic sponsors, it would be better to have a guidance from Agency.	

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)*
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

01 August 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
Gilead Sciences International Ltd

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1. General comments

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

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)*
608-610		Comment: Working week throughout the industry is Monday to Friday. This will be difficult to put into practice and will not add any value. It will however have a cost and resource implication given that changes will be required to SOPs, staff training and agreements (PVAs) with third parties. The industry generally accepts the need for cover over extended periods of absence beyond four days, so there would be minimal delays in reports retaining the original text and working to business days when received out of office hours. Proposed change (if any): Retain wording in previous version: "In practice this is the first business day the receiver becomes aware of the information."	
730		Comment: The title references interface with post authorisation studies but lines 733 through 736 define compassionate use, named patient use, etc. as post authorisation studies as opposed to solicited reports and this is confusing. Proposed change (if any): Clarify post authorisation studies clearly in terms of primary and secondary sources of data and remove reference to other solicited sources.	
739		Comment: Clarity is required on requirements for adverse events in post authorisation studies and why events and not	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		reactions are sufficient in the context of solicited reports if they remain under this section. Proposed change (if any): With regards to post authorisation safety studies (PASS): Each protocol should define the rationale for the safety data collection based on the purpose for the study, the knowledge of the drug and available data points available for the study. It is likely safety data generated from secondary sources of data will not have individual serious adverse drug reaction (SADR) collection, but reported in the clinical study report (CSR). Expedited reporting will apply as applicable in primary data collection studies and all safety data collected per the protocol will be reviewed and reported in the CSR from primary data studies.	
788 to 795		Comment: For studies with primary data collection, the events which are not actively sought per the protocol will not be available to the sponsor for inclusion in interim or final study reports, as they will not be actively collected in the course of the study – see proposed text above. Proposed change (if any): For adverse events actively sought according to the protocol, only valid ICSRs (see VI.B.2) of adverse reactions suspected to be related to the studied medicinal product should be reported (as solicited reports) by the sponsor to the competent authorities. With regards to the electronic	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		reporting of ICSRs, the recommendations provided in VI.C.6.2.3.7 should be followed. All other serious and non-serious reports of adverse events~~, which are not actively sought according to the protocol,~~ should only be summarised in the interim or final study report~~; they should not be reported as ICSRs to the competent authorities.~~	

Please add more rows if needed.

06.08.2013

Submission of comments on guideline on good pharmacovigilance practice Module VI (Rev1)

Comments from:

Name of organisation or individual
F.Hoffmann-la Roche

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1. General comments

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

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)*
		Comment: VI.C.1.2 – We request input from Licensing on the paragraph (lines 766-773) – do we have oversight of these study types? – Affiliates need to be made aware that these study types now need to be submitted. Clarification from EMA on the wording "influenced by" what does this include? Proposed change (if any):	
		Comment: VI.C.1.2.1 - We question the rationale regarding the concept of actively sought events versus non actively sought events. How should the actively sought events on the list be identified? How are emerging signals identified if only reported in interim/final study reports? The submission of specific drug/event pairs which could be NIS specific will be difficult. Will NIS protocols require updating for emerging signals throughout the study? How will oversight of all NIS protocols be co-ordinated for updates? Will Authorities request updates to actively sought events following interim/final study report review – will there be a situation where different Authorities require different events	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		(as per Ale) which will complicate the submission process further. Proposed change (if any):	
		Comment: VI.B.2 – Please clarify if reports of death where the cause of death has been requested but no follow up has been successful should be submitted? Currently all reports of death are submitted – we need to determine the requirements of the lines 409-412 which state "In this particular situation, medical judgement should always be applied in deciding whether the notified information is an adverse reaction or an event." Proposed change (if any):	
		Comment: VI.C.6.2.3.2 – should we submit clinical literature (or assume the sponsor will have done) Does clinical literature fall under the scope of module VI? Proposed change (if any):	
		Comment: VI.C.6.2.2.7 - Please confirm the LRD for data corrections where no new information is received can be the date the correction is confirmed/made (we do not need to go back to the LRD of the report where the error was made)	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		Proposed change (if any):	
		Comment: VI Appendix 1 Identification of biological medicinal products – the flow diagram requests follow up to identify batch number, brand name and active substance are present and identifiable for biological medicinal products. This information should be added to the case and if not available "document the missing required information in the case." Follow up needs to be completed and new or unavailable information documented. Proposed change (if any):	
		Comment: VI.C.6.2.3.7: reports originating from organised data collection systems and other systems. Section 1b – where the adverse reaction is only suspected to be related to a medicinal product which is not subject to the scope of the organised data collection system and there is no interaction with the studied (or supplied) medicinal product: the report should be considered as spontaneous report. For NIP cases it is difficult to know the scope of the organised data system and currently such reports are entered inconsistently as either solicited or spontaneous. 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')*	Outcome *(To be completed by the Agency)*

Please add more rows if needed.

August 5, 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
EORTC - European Organisation for Research and Treatment of Cancer

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)*
	It would be good to have guidance on reporting of Adverse events of special interest	

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)*
Lines 608-609		Comment: It is the first day when a receiver is informed of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday: EORTC question: What would be the reason for this change and are the implications of non-conformance been weighed?	
Lines 436-439		Comment: Causality and seriousness assessment is the responsibility of the primary source. The causality assessment of the receiver is not mandatory to be collected in a structured way and can be put in the narrative.	

Please add more rows if needed.

25 July 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products ' (EMA/873138/2011 Rev 1*)

Comments from:

Name of organisation or individual
EGA - EUROPEAN GENERIC MEDICINES ASSOCIATION

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The EGA welcomes this opportunity to comment on this GVP proposal incorporating new elements coming from the new pharmacovigilance legislation. Although we fully understand and support the intention of the proposed module, the EGA members have a few 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')*	Outcome *(To be completed by the Agency)*
224		….or to making a medical diagnosis [DIR Art 1**]** **and which is not a medical device**	
247		… friend **of a patient,..**	
768-770		A lot of academic research is partially (usually a small donation) financed. The addition gives confusion so the order of words should be changed. Proposed change: However when a study is directly **managed (fully or partially),** financed, initiated, ~~managed (fully or partially),~~ or where….	
780		More clarification should be given to the terminology "actively sought". In general non interventional studies where adverse events are actively sought could be considered as a PASS. This is not the intention of this paragraph – so further clarification should be given	
779 - 797		The requirements remain unclear. It is advisable to add the following sentence for clarification; **In non-interventional studies the named adverse events or groups of adverse events which are actively sought should be collected and reported. Other serious and non-serious adverse events should not be actively collected or requested but IF reported to the MAH**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		should be summarised in the final report	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<5th of August 2013>

Submission of comments on Module VI – Management and reporting of adverse reactions to medicinal products (EMA/873138/2011 Rev 1)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	EFPIA welcomes this update to Module VI; particularly the proposals to address the key issue of data collection from non-interventional studies, the clarification of some inconsistencies such as the definition of Day 0 and the maintenance of interim arrangements on a web page rather than VVI.App.3.1.1. of the Module. Despite this, there are additional sections of this Module which would benefit from revision which were covered in an EFPIA position paper which was shared with the EMA in May, some of these include: • VI.B.1.1.4. Collection and reporting of safety data from market research, patient support programmes and non-company sponsored websites, • VI.B.6.3. clarification of collection of off label use information • VI.C.6.2.3.7. classification of clinical study cases where the suspect drug is concomitant – these should be solicited, not spontaneous. • The terms adverse event (AE) and adverse reaction are used interchangeably in the Module and add confusion, e.g. paragraph 779-797. Consistent use according to the definitions in Annex 1 is needed to improve clarity. In Annex 1, an adverse reaction is '*a response to a medicinal product which is noxious and unintended*' and an AE is '*any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product*'. EFPIA would welcome a follow up consultation including the above points and additional ones in the May EFPIA paper before the end of the year.	

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')*	COMPANY COMMENT *(To be completed by the Agency)*
Line 198		We agree with the omission of the word 'patients' but for clarity, footer should be inserted at the first mention to make clear 'consumers' could be patients or other non-healthcare professionals (HCP). Proposed change (insert footer): ***The term 'consumers' includes all non-healthcare professionals, including patients.***	
Lines 609 and 610		Deletion of the sentence in lines 609 and 610 seems to suggest that the regulatory clock doesn't start when the receiver becomes aware but when the receiver is informed, i.e. the date of notification to the receiver. This doesn't take into account situations where AEs are not directly reported to the Company but perhaps sourced via Literature or Websites etc. The proposed change to the definition is aligned with the FDA interpretation of awareness. Proposed change: *It is the first day when a receiver* ***becomes aware*** *of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday.* ~~*In practice this is the first business day the receiver becomes aware of the information.*~~	
Line 768 to 773		The edits below are proposed for clarity and to align with wording used elsewhere in the guideline, e.g. in lines 352-354 regarding the phrasing on "company sponsored". We propose switching the "or" for "and" below to allow companies to fund investigator initiated studies (IIS) where they do not influence the design. To better align with the ICH E6 definition of a sponsor ("*An individual, company, institution, or organization which takes responsibility for 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')*	COMPANY COMMENT *(To be completed by the Agency)*
		initiation, management, and/or financing of a clinical trial"), it is proposed to change the word *influenced* to *controlled.*Proposed change: *However, where a study is directly financed, initiated, managed* ***~~(fully or partially),~~ ~~or~~ and*** *where its design is* ***~~influenced~~ controlled*** *by a marketing authorisation holder (voluntarily or pursuant to obligations imposed in accordance with Articles 21a or 22a of Directive 2001/83/EC), the* ***~~marketing authorisation holder~~ study*** *should be considered* ***~~as sponsor~~ company sponsored****. In this context, the marketing authorisation holder should fulfil the reporting requirements detailed in this Module.*	
Line 778		Combined study designs may have elements of primary and secondary data collection; propose inserted text below for clarity. Proposed change (inserted at end of line 778): ***Combined study designs may have elements of primary and secondary data collection.***	
Line 800		Proposed wording below is clearer. Proposed change: *For non-interventional study designs which are based on secondary use of data, the reporting of suspected adverse reactions as ICSRs is not required. Reports of adverse events/reactions should be summarised in* ***any safety interim analysis and*** *the final study report~~, where applicable~~.*	
Line 788 to 795		Over-reporting of adverse events by investigators is common in non-interventional studies and marketing authorisation holders will receive valid ICSRs from investigators that should not have been forwarded according to the study protocol. The proposed wording	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	COMPANY COMMENT *(To be completed by the Agency)*
		would not have allowed these valid ICSRs to be reported, and the edits below allow this flexibility, which would greatly reduce administrative burden for companies. Proposed change: ***~~For adverse events actively sought according to the protocol,~~ O****nly valid ICSRs (see VI.B.2.) of adverse reactions suspected to be related to the studied medicinal product should be reported (as solicited reports) by the sponsor to the competent authorities. With regards to the electronic reporting of ICSRs, the recommendations provided in VI.C.6.2.3.7. should be followed. All other* ***~~serious and non-serious~~*** *reports of adverse events,* ***~~which are not actively sought according to the protocol,~~*** *should only be summarised in the interim or final study report; they should not be reported as ISCRs to the competent authorities.*	
Lines 794-795		Typo: "ISCR" should be "ICSR". For clarity, we recommend the addition on the line below to line 795. Proposed change: *All other serious and non-serious reports of adverse events, which are not actively sought according to the protocol, should only be summarised in the interim or final study report; they should not be reported as* ***~~ISCRs~~ ICSRs*** *to the competent authorities..* ***Adverse event data to be included in periodic reporting (DSUR/ PSUR) as applicable.***	
Line 1525		The handling of languages can be problematic and it is important that requests for verbatim texts in Member State languages are consistent. The word shall in line 1525 should be replaced by the word 'may' to make clear that the inclusion of the original verbatim	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	COMPANY COMMENT *(To be completed by the Agency)*
		text in the ICSR is required only if requested by the Member State. Proposed change *Where suspected adverse reactions are reported by the primary source in narrative and textual descriptions in an official language of the Union other than English, the original verbatim text and the summary thereof in English* ***~~shall~~ may*** *be provided by the marketing authorisation holder.*	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5th August 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
Drug Safety Research Unit, Southampton, UK

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)*
	We have made some suggestions below in order to further clarify both the distinction between primary and secondary use of data and requirements for the reporting of adverse events not suspected by the reporter to be related to the medicinal product being studied.	

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)*
Line 766		Comment: Academic does not need a capital A. Proposed change (if any): The requirements provided in this Module do not apply to a~~A~~cademic sponsors, who should follow local	
Line 768		Comment: We suggest the insertion of an additional phrase in order to distinguish more clearly between primary data and secondary data. Proposed change (if any):However, where a study is a non-interventional study with primary data collection (see VI.C.1.2.1 below) and is being either~~is~~ directly financed, initiated, managed (fully or partially)…	
Line 777		Comment: We suggest the insertion of an additional phrase in order to clarify the definition of secondary use of data. Proposed change (if any): based on secondary use of data such as studies based on medical chart reviews, including intensive monitoring systems where the doctor is asked to provide information from the medical chart, sometime after the event, or electronic	
Line 780		Comment: We suggest that the term "non-academic" is not needed here, as this sentence applies to all sponsors . 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')*	Outcome *(To be completed by the Agency)*
		then agrees with line 771, such that irrespective of whether a study is conducted by a non-academic sponsor, the overall sponsor is the MAH. Proposed change (if any): or consumers, ~~non-academic~~ sponsors should specify in the protocol any adverse events (serious	
Line 786		Comment: We suggest that the term "efficacy" is not needed here. Proposed change (if any): be provided, for example because they represent outcomes of the study (~~efficacy~~ end point),	
Line 790		Comment: We suggest the insertion of "by the reporter" in order to improve clarity. Proposed change (if any): reactions suspected by the reporter to be related to the studied medicinal product should be reported (as solicited	
Line 791		Comment: We suggest the insertion of an additional sentence for the avoidance of doubt regarding reporting of adverse events actively sought according to the protocol, but not suspected by the reporter to be related to the medicinal product. Lines 789 to 791 imply that an adverse event not considered to be an adverse reaction suspected by 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')*	Outcome *(To be completed by the Agency)*
		reporter to be related to the studied medical product should not be reported, even if actively sought according to the protocol. This implies that they should be treated as per adverse events not actively sought (lines 792 to 795). Proposed change (if any): reports) by the sponsor to the competent authorities. Adverse events actively sought according to the protocol, but not suspected by the reporter to be adverse reactions related to the studied medicinal product, should not be reported as valid ICSRs. With regards to the electronic reporting of	
		Comment: Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<13/July/2013>

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

Comments from:

Dr Jürgen Beckmann, 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*).*

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1. General comments

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

A major problem is created by the omission of any differentiation between “expected” and “non-expected” ADRs in terms of reporting obligations (e.g. 603ff and 868ff). It can be anticipated that thousands or millions of reports addressing exactly what is well-known and documented in all relevant SmPCs, PILs and CCSIs will be sent around. There wouldn’t be any added value in terms of increasing the knowledge about the quality of these ADRs, nor would the reports add much knowledge about their numerical quantity (i.e. frequency), because the size of the underlying exposed patient population is not known. On the other hand, the workload would be immense, not the least because all non-serious ADRs will now also be included and because of the huge number of narratives or English narrative summaries from all over the world (lines 1526 – 1528). The balance of effort (manpower, time, costs) vs. gain for public health or science would be grossly unfavourable.

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)*
4	06	Comment: The main part of management starts after reporting Proposed change (if any): "Management" and "reporting" should be swapped	
185-189	06	Comment: It should be made clear whether abnormal laboratory findings are included. These may, as such, not be "noxious" but even physiologically sensible and desirable, e.g. leucocytosis in response to parenteral administration of a medicine with bacterial contamination. Likewise, it is not clear whether e.g. a threefold increase of transaminases in the absence of other symptoms which could warrant the diagnosis "hepatitis" should be considered as an ADR under this definition. Proposed change (if any):	
246-247	06	Comment: This definition of a consumer is not sensible: It is just in negative terms, i.e. "not a healthcare professional" and built on examples	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		The absurdity of this definition (and in the "Definition"-document from which it is copied) can be demonstrated by putting the (reverse) question: "What is a lawyer, friend or relative of a patient but not a healthcare professional?" Nobody would even think of answering "a consumer". Proposed change (if any): There should be at least a positive element, such as "a person which is reasonably likely to become exposed to certain medicines". And healthcare professionals should not be excluded but rather regarded as a specific subgroup among consumers. After all, they also can fall ill and become patients in need of medicines.	
253-257		This paragraph correctly makes a difference between a patient or consumer report on the one hand and a healthcare professional report on the other. However, in the following part of the document it does not seem that any differential "management" is recommended or required.	

262	Malignancy should be included in the definition of seriousness at this place as well – not just in further comments (lines 269-270). According to the core definition of "seriousness" in the first paragraph a malignant transformation of cells or cancer in situ may not fulfill the core criteria listed here.
345-349	Obliging a company to make "every attempt" to "obtain the minimum information that constitutes a valid ICSR" seems inappropriate and not worth wile in many cases of reports from non-medical sources, e.g. in the event of a flood of media-triggered incomplete consumer reports about non-serious AEs/ADRs.
351-356	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). See also comment to lines 905–907.
397	The list of information characterizing 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.
572-578	Expedited reporting does not seem appropriate in all cases included here. Thus, there wouldn't be a point in expedited reporting of a non-serious ADR (e.g. slight hangover) related to slight overdose (e.g. 30% higher than the maximum recommended dose of an hypnotic).
567 and 1391-1422	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 judgment about relatedness between

	medication and adverse event (creating a reportable ICSR) it is always crucial whether or not just the fact that the medicine was used other than officially recommended/authorized created the adverse event, and if so: What the cause of the deviation from what is recommended/authorized might have been (root-cause-analysis). It should be kept in mind that some kind of deviation from "standard" underlies about every second ICSR and is worth analyzing.
375, 582, 583	"Efficacy" should be replaced by "effectiveness".
586	After "time frame" it should be added "in particular if lack of effectiveness was unexpected"
602ff	A paragraph should be included here addressing the reporting of lack of effectiveness in case of suspected quality defect or counterfeiting. This deficit is not sufficiently compensated in Section C (lines 972–973).
1017-1043	The whole section VI.C.2.2.6 should be omitted. All the examples are either no reportable ICSRs anyway (e.g. lack of supply of medicines) or they are terms which do not explicitly describe but also not exclude the possibility that the underlying information is just a reportable ICSR (e.g. "safety issues published in the scientific literature" or "safety issues related to the use outside the terms of the marketing authorisation").
1185-1187	It is not for this guideline to state which obligations of member states vs. WHO are omitted or replaced. There are bilateral binding agreements between EU Member States and WHO which cannot be nullified or replaced ed by such a guideline.

1391-1422 See comments to line 567

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05.08.2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	With reference to sections VI.C.1.1. and VI.C.1.2, clarification is needed if a sponsor of a clinical trial or post-authorisation study is not compliant with GVP VI and forwards cases that are not supposed to be notified to a MAH. In particular: cases, where either IMP(s) (scenario 1) or both, IMP(s) and NIMP(s) (scenario 2), are suspected, and the MAH (these cases were forwarded to) is owner or cannot exclude its ownership (MAH unknown) of IMP(s) or NIMP(s), respectively. According to Volume 10 Clinical trials guidelines ('CT-3') (2011/C 172/01): "safety reporting falls either under Directive 2001/20/EC or under the provisions on pharmacovigilance as set out in Directive 2001/83/EC and Regulation (EC) No 726/2004. Adverse reactions may not be reported under both regimes, i.e. Directive 2001/20/EC as well as Regulation (EC) No 726/2004 and Directive 2001/83/EC." Thus, can or should the MAH, who is owner (or whose ownership cannot be excluded) of IMP(s) or NIMP(s) (in terms of scenario 1 and 2, as described above), disregard these cases, as their inclusion in the MAH's PV database as spontaneous reports and their consequent inclusion in the PSUR (Module VII) is in conflict with 2011/C 172/0 and inevitably leads to duplicates?	

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)*
766 - 773		**Comment**: In this section it is mentioned, that marketing authorization holder should be "considered as sponsor", if the study is directly financed, initiated, managed (fully or partially) or where its design is influenced by a marketing authorization holder; in this case the marketing authorization holder should fulfill the reporting requirements detailed in this Module. As the term "sponsor" is defined (Directive 2001/20/EC, ICH E6) we are wondering what kind of obligations a "considered sponsor" needs to meet? **Proposed change (if any):** As a general rule, a study should have a single sponsor to avoid any confusion regarding responsibilities of the sponsor of a study. In all cases where sponsor obligations as to financing and as to GCP are planned to be met by different persons or organisations we recommend the following wording (line 768 ff): However, where a study is directly financed, initiated, managed (fully or partially), or where the its design is influenced by a marketing authorisation holder (voluntarily or pursuant to obligations imposed in accordance with Articles 21a or 22a of Directive 2001/83/EC), ~~the marketing authorisation holder should be considered as sponsor. In this context, the marketing authorisation holder should fulfil the reporting requirements detailed in this Module.~~ it should be agreed on the responsibilities in a written agreement between the parties.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 august 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

Name of organisation or individual
Agence nationale de sécurité du médicament et des produits de santé French National Agency for Medicines and Health Products Safety 143-147 boulevard Anatole France 93285 Saint-Denis Cedex France

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	Outcome *(To be completed by the Agency)*
ANSM	Amendments proposed for the GVP – module VI, especially regarding the management of the adverse events reported in non-interventional studies appear unacceptable. Indeed, any adverse events not specifically defined as "actively sought" in the protocol of the study would not be considered as potential "ICSRs" anymore and will only be summarised in the interim or final study report. To our mind, it is against the "spirit" and the goal of pharmacovigilance. Indeed, as mentioned in the Directive 2010/84/EC amending the Directive 2001/83/EC: - Art 107, 1°: 1. "Marketing authorisation holders shall record **all suspected adverse reactions** in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or **occurring in the context of a post-authorisation study**." - Art. 107, 3°: "Marketing authorisation holders shall **submit electronically** […] **information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days** following the day on which the marketing authorisation holder concerned gained knowledge of the event." and "Marketing authorisation holders shall **submit electronically** to the Eudravigilance database **information on all non-serious suspected**	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	<u>adverse reactions that occur in the Union, within 90 days</u> following the day on which the marketing authorisation holder concerned gained knowledge of the event." In addition, the aim is also to **continuously monitor pharmacovigilance data**, whatever the source. This should be based on all available data, as in the above mentioned Art 107. Even though a non-interventional study could aim to more precisely specify an already identified safety issue, non-interventional could also aim to confirm a global safety profile in "real use" or to obtain "long-term safety data" or to monitor/identify rare/very rare ADRs not previously identified in clinical trials... Limiting the reporting of ICSRs to ADRs predefined in the study protocol would potentially lead to a loss of information or a delay in safety assessment or safety measures (especially if the ADRs are serious). This would be inconsistent with the obligations of Article 107 of Directive 2001/83/EC as amended and the obligation to continuously monitor pharmacovigilance data. In addition, these requirements are inconsistent with those applicable to Academic sponsors who should follow local requirements as regards the reporting of cases of suspected adverse reactions to NCA.	

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)*
735 - 804	?	Comment: see the general comment Proposed change (if any): The paragraph regarding reporting of primary data from non-interventional studies (from lines 779 to line 797) should not be amended. The ADRs reported in the non-interventional studies should follow the requirements applicable to spontaneous reports (all serious cases should be considered as ICSRs to be reported) and all cases should be summarised in the interim or final study report. An additional recommandation could be included (or included in module VIII), i.e : In each non-interventional study protocol, a wording aiming the MAHs to encourage healthcare professionals or consumers to specifically report any adverse events actively sought (if some exist) should be included.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 August 2013

Submission of comments on 'GVP Module VI – Management and reporting of adverse reactions to medicinal products' – Revision 1 (EMA/873138/2011)

Comments from:

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

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

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1. General comments

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

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)*
617 to 618		Comment: For ICSRs from local journals in other language than English the initial reporting to the authority does require the minimum criteria only. Date of receipt of the translated abstract or article is assessed as follow- up.	
788 to 795		Comment: It might be clarified that only ADR and not AE should be collected. Collection of AE in non-interventional studies would be a significant workload increase for the MAHs. Moreover, over-reporting of adverse events by investigators is common in non-interventional studies and marketing authorisation holders will receive valid ICSRs from investigators that should not have been forwarded according to the study protocol. The edits below allow more flexibility, which would reduce administrative burden for companies. 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')*	Outcome *(To be completed by the Agency)*
		~~**For adverse events actively sought according to the protocol,**~~ Only valid ICSRs (see VI.B.2.) of adverse reactions suspected to be related to the studied medicinal product should be reported **from company sponsored studies** (as solicited reports) by the ~~**sponsor**~~ **holder** to the competent authorities. With regards to the electronic reporting of ICSRs, the recommendations provided in VI.C.6.2.3.7. should be followed. All other ~~**serious and non-serious**~~ reports of adverse events, which are not actively sought according to the protocol, should only be summarised in the interim or final study report **as determined by the protocol of the study**; they should not be reported as ICSRs to the competent authorities.	