13 December 2012
EMA/806364/2012
Patient Health Protection

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

GVP Module IV – Pharmacovigilance audits

The draft of this module was released for public consultation between 26 July and 21 September 2012. 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.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8668
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2012

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
AESGP

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

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*).*

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We very much appreciate the risk-based approach to pharmacovigilance audits. Overall, this module seems to be different from other modules, probably by using terms that are normally not used in the other modules or in the context of pharmacovigilance. Example: In this Module the term "senior management" is used very often whist in Module I the term "upper management" is used. Not all terms marked with a star (*) are explained in the glossary, e.g. routine quality control (line 250).
	Only under section IV.C.1.1.2 is there a mention of the QPPV's responsibilities. In order to reinforce the responsibilities of the QPPV it would be more appropriate to include reference to them in many other parts of the guideline e.g. IV.B.2 – the strategic level audit planning bullet mentions that this should be endorsed by senior management, but often the QPPV is not necessarily senior management and therefore should be named in this section. The document appeared to have sparse mention of the QPPV, yet they should be considered a key player in the planning and execution of PV audits.

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')*
174		Comment: Please clarify "head of the organisation". Is this the head of quality or the QPPV?
206 + 334		Comment: Please clarify if audit recommendations are to be graded. If they are graded, how do audit recommendations differ from audit findings?
230		Comment: The adjective "serious" in "serious concerns" should be explained. Does it mean "critical" findings"? If yes, this expression should be used instead. Please also provide information regarding a possible timeframe for the terms "urgently" and "expedited".
236-240		Comment: "*Senior management […] should ensure that effective action is implemented […] or formally accept the risk of not taking actions.*" This sentence is inconsistent with lines 335-337: *"Bases on the audit findings the MAH shall ensure that an appropriate plan detailing corrective and preventive action is prepared and implemented."* This sentence should be reworded as the possibility of accepting the risk of not taking action may be difficult to accept for the QPPV who, at the end, has to fulfil its tasks and responsibilities and will be the one being pursued in case of issues – not the senior management or those charged with governance.
248-265		Comment: Regarding the independency the wording of the IR 13(1) is the following: … *"Those (quality) audits shall be conducted by individuals who have no direct involvement in or responsibility for the matters or processes*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		being audited." However Module IV states that *"Pharmacovigilance audit activities should be independent and separate from routine quality control activities relating to pharmacovigilance."* Whilst the independency requirement may be met in large companies with sufficient personnel, this might prove much more challenging in smaller or medium-sized companies, which may not have the possibility to hire separate, qualified and experienced staff for audits in pharmacovigilance (as requested in section IV.B.3.1.2). For smaller and medium-sized companies it should be possible, for example, that pharmacovigilance personnel of one affiliate (site) audits the another one. Another possibility would be that personnel from a non-pharmacovigilance department perform this audit, provided they have the necessary knowledge about pharmacovigilance.
266-277		Comment: Concerning the qualifications, skills and experience of the auditors and continuing professional development, the following requirements should be sufficient: - audit principles, procedures and techniques; - applicable laws, regulations and other requirements relevant to pharmacovigilance; - pharmacovigilance activities, processes and system(s). Proposed change (if any): Please reword accordingly
279-280		**Comment:** Please provide guidance on the type of metrics to be used to evaluate the audit work.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
307-309		**Comment:** Please provide guidance on the QPPV's involvement (role and responsibilities) in strategic level audit planning and tactical level audit planning.
332-343		Comment: According to Section IV.C.2.1, the MAH shall place a note concerning the main audit findings and audit recommendations including critical and major audit findings/audit recommendations of any audit relating to the pharmacovigilance system into the PSMF. According to Module II (PSMF), critical and major finding **together with a note of corrective and preventive actions** should be placed in the Annex of the PSMF. If with "recommendations" "corrective and preventive actions" are meant, the latter wording should be used. If not, the recommendations should be deleted from the draft.

Please add more rows if needed.

21.09.2012

Submission of comments on 'good pharmacovigilance practices module IV – Pharmacovigilance Audits" (EMA/228028/2012)

Comments from:

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

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

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	In principle a risk-based approach to pharmacovigilance audits is welcomed. Regarded literally the complete module seems to be different from other modules, probably by using terms that are normally not used in the other modules or in the context of pharmacovigilance. Example: In this Module the term "senior management" is used very often. In Module I the "upper management" is mentioned in several sections. If "senior" means the same as "upper" the wording should be adapted to Module I. Not all terms marked with a star (*) are explained in the glossary, e.g. routine quality control (line 250).

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')*
79		**Comment**: Typing error: provides "an" instead of provides "and".
230		**Comment**: The term "serious" concerns should be explained. Does it mean "critical" findings". If yes, this expression should be used.
236 ff and 335 ff		**Comment**: Senior management (of an organisation) should either ensure that effective action is implemented … or formally accept the risk of not taking actions. This possibility of accepting the risk of not taking any actions is not acceptable for the QPPV who at the end has to fulfil tasks and to take responsibilities. Therefore, the sentence should end after the words "pharmacovigilance audits". It is furthermore inconsistent with line 335 ff: "Bases on the audit findings the MAH shall ensure that an appropriate plan detailing corrective and preventive action is prepared and implemented." If in line 236 the senior management of a MAH is excluded from the possibility to formally accept the risk of not taking actions this should be indicated clearly.
248 ff		**Comment**: Regarding the independency the wording of the IR 13(1) is the following: … "Those (quality) audits shall be conducted by individuals who have no direct involvement in or responsibility for the matters or processes being audited."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		However Module IV states that "Pharmacovigilance audit activities should be independent and separate from routine quality control activities relating to pharmacovigilance." This independency might be achieved in large companies with sufficient personnel. In smaller or medium sized companies however it is not possible to employ separate staff for audits in pharmacovigilance especially in conjunction with the requirements in IV.B.3.1.2 regarding qualifications, skills and experience (line 266 ff). For smaller and medium sized companies it should be possible e.g. that pharmacovigilance personnel of one affiliate (site) audits the another one. Another possibility would be that personnel from a pharmacovigilance independent department performs this audit, provided they have the necessary knowledge about pharmacovigilance.
248 ff		**Comment**: Regarding the independency the wording of the IR 13(1) is the following: … "Those (quality) audits shall be conducted by individuals who have no direct involvement in or responsibility for the matters or processes being audited." However Module IV states that "Pharmacovigilance audit activities should be independent and separate from routine quality control activities relating to pharmacovigilance." This independency might be achieved in large companies with sufficient personnel. In smaller or medium sized companies however it is not possible to employ separate staff for audits in pharmacovigilance especially in conjunction with the requirements in IV.B.3.1.2 regarding qualifications, skills and experience (line 266 ff). For smaller and medium sized companies it should be possible e.g. that pharmacovigilance personnel of one affiliate (site) audits the another one. Another possibility would be that personnel from a pharmacovigilance independent department performs this audit, provided they have the necessary knowledge about pharmacovigilance.
266 ff		Concerning the qualifications, skills and experience of the auditors and continuing professional development, 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')*
		following requirements should be sufficient: - audit principles, procedures and techniques; - applicable laws, regulations and other requirements relevant to pharmacovigilance; - pharmacovigilance activities, processes and system(s).
333 ff		**Comment**: According to Section IV.C.2.1 the MAH shall place a note concerning the main audit findings and audit recommendations including critical and major audit findings/audit recommendations of any audit relating to the pharmacovigilance system into the PSMF. According to Module II (PSMF) critical and major finding **together with a note of corrective and preventive actions** should be placed in the Annex of the PSMF. If with "recommendations" "corrective and preventive actions" are meant the latter wording should be used. If not, the recommendations should be deleted from the draft.

21 September 2012

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
Celgene Europe Ltd

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

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).

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	This module refers to "audit recommendations". There is however, no clarity on under what circumstances these are expected to be given and if they are expected for all (Critical, Major, Minor) findings or are given at the discretion of the auditor. As auditors are not the Subject Matter Experts (SMEs), they are not always best placed to determine robust resolution for findings. Providing recommendations upfront for a finding could encourage auditees to limit their response based on the recommendation provided by the auditor and this could be detrimental to the audit program and its intent. It would be beneficial to clarify that audit recommendations should be provided at the discretion of the auditor and in circumstances when the auditee may wish to work with the auditor to ensure that the proposed CAPA would address the finding sufficiently or if they are unsure of what kind of CAPA to implement. Reference to audit recommendations should be removed from the grading system definitions and, if required, a general statement on their aims should be included in the relevant section.

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')*
46 &51		**Comment:** The term "audits of their quality systems" is not clear. **Proposed change:** In line with article 108(b) of the Directive it should be amended to "audits of their quality systems for the performance of pharmacovigilance activities"
54-55		**Comment:** "all areas listed in Directive 2001/83/EC (DIR) and Regulation (EC) 726/2004 (REG)" is not really clear as both documents contain a lot of areas not relating to pharmacovigilance. **Proposed change:** The sentence should be amended to read "Risk-based audits of the pharmacovigilance system contain all areas listed in Title IX of the Directive 2001/83/EC (DIR)." In line with the definition of the pharmacovigilance system.
90		**Comment:** The term "criteria" should be expanded for clarity **Proposed change:** "determine the extent to which the **audit** criteria are fulfilled"
121		**Comment:** Please clarify the term "audit themes" and provide some examples. Does this refer to the audit type i.e. affiliate, systems etc. or scheduled, follow up or ad hoc audits or the audit focus such as compliance or effectiveness etc. or all these?
123		**Comment:** Please clarify the term "internal controls". Is this in the context of the definition of "Controls" in the Glossary i.e. management actions or to do with processes and procedures that apply to pharmacovigilance activities?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
136		**Comment:** Please clarify the term "key managerial functions". Does this refer to management functions related only to PV or include management changes for all departments and at the global and local levels?
138		**Comment:** Please clarify how the terms "recent re-organisation" and "recent increase in volumes of work" relate to the 3 – 5 year strategy which is a high level and long term plan. **Proposed change**: Remove reference to "recent"
162		**Comment:** Please specify what "complaints" are being referred to here. Is it just product complaints or includes other kinds of complaints also. **Proposed change**: Change to state "from **product** complaints"
168		**Comment:** Please specify what "complaints" are being referred to here. Is it just product complaints or other kinds of complaints also **Proposed change:** Change to state "from **product** complaints"
174		**Comment:** Please clarify reference to "head of the organisation". Is this the Manager of the department responsible for audits or higher up? How high up in the organisation does this person need to be? Please be more specific on the role of this person.
201 - 204		**Comment:** See comments under "General Comments" above. More clarity is required around the intent and use of audit recommendations.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Clarify use and intent of providing audit recommendations and remove reference to audit recommendations from the grading system definitions. If required provide a general statement on their aims in the relevant section.
230 - 231		**Comment:** The term "serious concern" is not clear. **Proposed change**: It should be defined in the context of the classification of findings (e.g. critical findings) as outlined above in this section.
236 - 238		**Comment:** Please clarify the expectations as far as "formally accepting the risk of not taking action". For example, does this have to be documented in a Form or other such document or is an email sufficient documentation? Also does this apply to all findings (critical, major, minor) or just critical and major? Please clarify if audit recommendations require "formal acceptance of the risk" of they are not implemented.
239 - 240		**Comment:** It is stated that progress of implementation of agreed actions should be communicated to senior management but it is not clear if this is the responsibility of the auditor, auditee or both to provide to their individual management.
284 - 294		**Comment:** Please provide some clarity on whether this section applies to an independent Consultant used to perform an audit and write a report. Can the company use discretion as to what level of information is relevant to provide on a case by case basis?
307-309		**Comment:** Please clarify the intent of "including knowledge of status of corrective and preventative actions." The QPPV cannot be expected to know the status of all corrective and preventative actions and should also be able to seek information from the auditors on the status of corrective and preventative actions, especially if it, for example, concerns vendor audits.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Provide here for the QPPV to also be able to seek this information from the auditors.
333-335		**Comment:** Audit recommendations are not covered by the IR or DIR and Module II only requires a brief description of the CAPA. **Proposed change:** Remove reference to placing a note concerning the audit recommendations in the PSMF.
339 - 340		**Comment:** This sentence should be aligned with Module II: **Proposed change:** "The note and associated corrective and preventative action(s), shall be documented in the pharmacovigilance system master file until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified [DIR Art 104(2)]."

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17th August 2012

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
Dr. Ebeling & Assoc. GmbH, Pharmacovigilance Service Provider

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).

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	A yearly audit of the Pharmacovigilance system should be implemented.
	ISO 19011-2011 implemented the Remote Audits. This should be also implemented in the GvP-Module, i.e. with focus on the audits of contractual partners.
	In general, audits of contractual partners are not mentioned sufficiently.

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')*
117-199		Comment: There are three drafted planning phases described for GvP audits. ISO 19011-2011 describes only two planning phases. Proposed change: Strategical and Tactical audit planning should be summarised as Audit Programme and Operational level audit planning should be the individual Audit Plan.
120-121		Comment: "Training Needs" is not determined. Proposed change: "Training Needs" should be removed from this chapter and to be described in a specific chapter of this GvP-Module. If "Training Needs" is focussed on the qualification of PV auditors, a specific chapter on the selection and qualification of audits should be implemented outlining that auditors have to be trained according to their role. This is also outlined in ISO 19011-2011.
174		Comment: The GvP-Module outlines that the Head of Organisation should approve the audit programme. ISO 19011-2011 states that the person responsible for the audit process should approve the audit programme. Nevertheless, ISO 19011-2011 also states that the person responsible for the audit process should inform the Head of Organisation on the content and to request an approval, if applicable. Proposed change: It should be described that the QPPV, as responsible person for Pharmacovigilance audits, should lead and approve the audit programme, and selects the auditors. It should be also outlined that the QPPV could not be an auditor during internal PV audits, but that the QPPV could be a participating expert supporting the auditors.
174+231		Comment: Line 174 mentions the Head of Organisation, Line 231 the Senior Management. Proposed change: Unique terms should be used.
192-199		Comment: ISO 19011-2011 describes the check of documentation previous to the audit.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: The previous check of documentation should be also part of GvP audits. Especially the time to audit a contractual partner could be shortened, if documentation would have been checked in advance.
192-199		Comment: ISO 19011-2011 mentions the preparation of an individual checklist for the audits. This is not mentioned in the GvP-Module. Proposed change: The preparation of an individual checklist for the audits should be also mentioned in the GvP-Module.
192-199		Comment: Chapter IV.B.2.3.1 only describes the Planning of GvP audits but not the Fieldwork. Proposed change: It should be mentioned at least to conduct an opening and a closing meeting, and furthermore to use interviews and documentation review to identify and assess risks.
201-231		Comment: There is no advice to handle or document the audit report. Proposed change: It should be mentioned in chapter IV.B.2.3.2. that a procedure determines, where the audit report should be kept and who should have access to the audit report, i.e. the QPPV.
212-229		Comment: The GvP-Module only describes three classifications of Nonconformity (critical, major, minor). ISO 19011-2011 outlines as audit findings the classification of Conformity and Nonconformity (and furthermore to make different classifications of nonconformity). Proposed change: Conformity should be also considered for GvP audits as a classification term of audit findings.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 September 2012

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
EFPIA

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*).*

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	EFPIA welcome the opportunity to provide comments on this draft GVP module IV on pharmacovigilance (PV) audits. The module is well structured and the content appropriately describes the basics for such audits. We particularly welcome the development of the risk-based approach requested in the Implementing Measures. Overall this document provides clear guidance on planning and conducting audits which will help promote standards and harmonisation throughout the European network. It is well written and thus comments of the EFPIA companies are minimal. As a general comment we note that there is no specific recommendation regarding contractors or licensing partners of MAH, this is interpreted as they should be part of audit planning using the risk based approach.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 43-44		*Comment:* The introduction states that the requirement for MAHs to perform audits of their pharmacovigilance system follows the entry into force of the new legislation; actually, such requirements were already existing (Vol 9A, 2.2.3.h, details required in the DDPS). *Proposed change:* "~~Following~~ The entry into force of the new legislation on pharmacovigilance in July 2012, ~~there is a~~ **emphasized the** requirement for MAHs~~, competent authorities in the Member States and the EMA~~ to perform audits in their pharmacovigilance systems, including risk based audits of their quality systems **and set up such requirements for competent authorities in the Member States and the European Medicines Agency (the Agency)."**
Line 55		*Comment:* Despite the sentence in lines 48-50, it remains unclear if the wording "contain all areas listed in Directive 2001/83/EC" stands only for Pharmacovigilance areas or also for related activities such as medical information (Dir art 98) or advertising (Dir title VIII) *Proposed change:* The wording "all areas listed" should be clarified to read **"all pharmacovigilance related areas listed in Dir…"**
Line 79		Comment (editorial): Section IV.C. provides 'and' outline of the operation of the EU network Proposed change: Section IV.C. provides an outline of the operation of the EU network
line 119		Comment: EFPIA companies have different interpretations of what is meant by "audit strategy" and therefore of what should be the period of time covered by this strategy. This reflects some lack of clarity in the recommendation. If the audit strategy is an overall plan from which the tactical plan is derived, a period of 3-5 years seems too long, as the experience shows that it is not realistic to plan audits beyond 2 years. There may be some types of audits routinely planned every 3/4 years (e.g. major affiliates), but this would be mentioned in an SOP, not in a formal audit planning. If the period of the strategic plan is meant to be the time expected for assurance of the whole PV system, then 3-5 years seems reasonable. In view of the pace of changes in the environment, a 5 year strategy will likely have to undergo substantial amendments. Here a three year strategy would be sufficient.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Clarify the period cover by the audit strategy
Lines 123-171:		Comment: We agree that the company should consider the audit activities from a strategic point of view and look into the next 3-5 years. However, many considerations listed in section IV.B.2.1 should rather go into the considerations to be taken when setting up an annual audit plan. Proposed change: Move some of the provided examples (e.g. risk to availability of adequately trained an experienced pharmacovigilance staff) to section IV.B.2.2 (Tactical level audit planning).
Lines 184-185		Comment: The scope and objectives of individual audits seem more appropriate for the operational level audit planning than for the tactical level planning. Indeed, as the scope and objectives are described in the notification letter, it is proposed to put only the title of the audit and the system to be audited instead of given details on the scope Proposed change: Move the scope and objectives of individual audits to section IV.B.2.3 (Operational level audit planning). "The audit programme document should include a brief description of the plan for each audit to be delivered (audit title, system to be audited) ~~including its scope and objectives~~."
Lines 192-193		*Comment:* There could be valid reasons why a planned audit cannot be conducted in the scheduled timeframe or has to be cancelled. Such possibility should be described and requirements (e.g. Documentation, reason) should be set forth. *Proposed change:* Add the following sentence: **"Changes to the audit programme may happen and will require proper documentation including reason for change, new timeframe."**
Lines 212-229		*Comment:* There is a need to ensure that the QPPV has impact to implement corrective actions which are beyond pharmacovigilance but still related to patient safety.
Line 241		Comment: "Evidence of completion of actions should be recorded in order.....". Consistent with the above comment, focus on significant findings. Proposed change: Evidence of completion of actions *from significant findings* should be recorded in order.....
Lines 307-311		Comment: the text states: "The responsibilities of the QPPV in respect of audit are provided in Module I. Furthermore, the QPPV should receive pharmacovigilance audit reports, and provide information to the auditors

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		relevant to the risk assessment, including knowledge of status of corrective and preventative actions. The QPPV should be notified of any audit findings relevant to the pharmacovigilance system in the EU, irrespective of where the audit was conducted." The formulation is too vague about the role of QPPV. To be consistent with GVP Module I, we suggest the following amended wording: Proposed change: "The responsibilities of the QPPV in respect of audit are provided in Module I. Furthermore, the QPPV should receive pharmacovigilance audit reports, and ~~provide information to the auditors relevant to the risk assessment, including knowledge of status of corrective and preventative actions. The QPPV~~ should be notified of any audit findings relevant to the pharmacovigilance system in the EU, irrespective of where the audit was conducted. *The QPPV should have access to the corrective and preventive action plan following each audit relevant to the PV system, so that the QPPV can ensure that appropriate corrective actions are implemented. The QPPV should be involved in the schedule of audits."*
lines 335 to 340		**Comment:** Two different modules have slightly different wording; therefore, clarification is needed on the trigger for 'the note' to be removed from the PSMF. • There appears to be three routes that a note can be removed per Module II: (i) once corrective action and/**or** (ii) sufficient improvement can be demonstrated **or** (iii) has been independently verified • Module IV adds in the concept of "objective evidence" but leaves interpretation open. ***Module II:*** "The note and associated corrective and preventative action(s), shall be documented in the pharmacovigilance system master file until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified [DIR Art 104(2)]." ***Module IV:*** "Once the corrective and preventative actions have been fully implemented, the note may be removed [DIR Art 104(2), IR Art 13(2)]. Objective evidence is required in order that any note of audit findings can be removed from the pharmacovigilance system master file (see Module II)." 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')*
		More clearly define the steps by which the note is removed.
Lines 341-342		Comment: "The marketing authorisation holders should ensure that they comply with reporting commitments in line with the legislation, GVP guidance and their internal reporting policies." Is this referring to IV.B.2.3.2 Reporting? Proposed change: Please supply the reference.
Lines 365-403		Comment: The "Glossary of Terms" contains some useful terms, but suggest including 'Recommendations' & 'Objective evidence.'
Line 371		Comment and proposed change: Add definition for "Audit programme" to differentiate it from "audit plan"

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 September 2012

Submission of comments on 'GVP Module IV Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
EGA - EUROPEAN GENERIC MEDICINES ASSOCIATION Rue D'Arlon 50 B-1000 Brussels Belgium

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	The EGA welcomes this opportunity to comment on the 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.
	In general, this module is a bit confusing, especially in the strategic level audit planning. An example may be required as an explanation. The risk-based approach requires an objective and precise method to do this calculation or at least a suggestion on how MAHs may do and evaluate the risk. Also an example or a better clarification would be required.
	In order to enable the head of Pharmacovigilance and drug safety in a company to correct audit findings in a best way and being compliant with all regulations and guidelines, the Head of Pharmacovigilance and Drug safety has to be in high level position in the company, preferred directing reporting line to CEO.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 105-106		Comment: It shouldn't be referred who should endorse strategic level audits, as companies have differences in their organisations and therefore, it should not be stated that way. Proposed change (if any): Removal of "which should be endorsed by senior management".
Line 174		Comment: It is written that the audit programme should be approved by the head of the organization. It is not clear who this person is. For example, a CEO will-should not sign the plan. The audit program should be risk-based and flexible in changes due to the identified risks. Proposed change (if any): audit programme should be approved by the PhV-compliance management.
Line 179		Comment: "Audit programme" should have a definition in the Glossary of Terms. Proposed change (if any): Add definition.
Line 184		Comment: The audit programme document should include a brief description of the plan for each audit to be delivered, including its scope and objectives. An audit programme is an annual plan and it does not make sense to include a brief description of the plan for each audit a year before the audit takes place. Each audit plan should be created before every audit. If this document is prepared in advance, many things might have changed which make the process very inefficient. Proposed change (if any): The audit plan for each audit needs to be written/prepared before each audit.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 187-189		Comment: It is not clear what "regular intervals" means. According to the Commission Implementing Regulation No. 520/2012 (article 13/1) – "risk-based audits of the quality system shall be performed at regular intervals". However there is the following statement: "audits of the quality system shall be performed at regular intervals, and not less than every two years" in the Concept Paper (Implementing measures in order to harmonise the performance of the pharmacovigilance activities provided for in directive 2001/83/EC and regulation (EC) no 726/2004). Proposed change: It would be good if they clarify what would be the regulatory expectations for "regular intervals".
Lines 193 – 194		If possible to clarify what are "all the steps" for which we have to establish timeframes?
Line 214, 221		Comment: definition of "risk to public health" is missing. Proposed change: Define the "risk to public health" in the Glossary of Terms or refer to a definition.
Line 214 - 215		Comment: A serious violation of a guideline can't be in all circumstances a "critical finding". Guidelines do not include only legally binding interpretation of the law but also recommendations, views of authorities, etc. A critical finding should only reflect violations of the law. Proposed change (if any): delete "and guidelines".
Line 252		Comment: "*In order to be independent, audits should be conducted by those who have no actual or potential conflicts of interest and who are not operationally involved in the activities to be audited"* There is always a potential conflict when the auditor is a company employee.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): We suggest deleting the word "potential" as there is always potential conflict when the auditor is a company employee: "*In order to be independent, audits should be conducted by those who have no actual or ~~potential~~ conflicts of interest and who are not operationally involved in the activities to be audited"*
Line 257		Comment: Head of organization is not directly interested with PhV activities. Proposed change (if any): It would be more realistic to have 2 lines to the Head of Pharmacovigilance and the head of Compliance. The main reporting line should be to the level within the organisation that allows the auditor(s) to fulfil their responsibilities.
Lines 309, 337,		Comment: According to ISO9000, it should be use the terminology "preventive actions" instead of "preventative actions" in GVP to maintain consistency with the ISO standards. Proposed change (if any): Change to "preventive" actions.
Line 339		Comment: Will the statement from the audited site that the corrective actions are completed be enough? Proposed change (if any): Please clarify "objective evidence"
Lines 351-352		Comment: The agency shall report the results of its pharmacovigilance system audits on a 2-yearly basis, but when can the first report be expected? Proposed change (if any): Clarification is required in line with transparency.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 360-363		Comment: The European Commission shall make a report on the performance activities on pharmacovigilance tasks by competent authorities in member states on 21-07-2015. Why is the report so late if competent authorities in member states have to report their results on 21-09-2013 at the latest? This is a very long period where significant changes may occur. Proposed change (if any): Clarification is required.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24th September 2012

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
EQAC – European Quality Assurance Confederation

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).

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Regarding the risk-based approach to pharmacovigilance audits, if a company already has an operating risk based approach methodology for audit planning, will they be expected to amend it to mirror the levels (strategic, tactical, operational) outlined in this module? If so, please provide the rational.
	Does the reference to 'recommendations' apply only to internal audit, or will government inspectors to also make recommendations in the future?

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')*
120		Comment: **Please explain the intent to this line regarding resource and training. Does this refer to resource and training of the auditors?** Proposed change (if any):
201		Comment: **Please explain the rational for requiring that QA give 'recommendations' in a formal audit report in addition to findings. QA are not the Subject Matter Experts, are independent of the process and as such are not best placed to recommend corrective actions. If QA give formal recommendations in an audit report please be aware this may compromise future audits as the business may just cite the previous QA recommendation in defense of a new finding.** Proposed change (if any):
207		Comment: **Please give further guidance on the concept of grading recommendations in addition to audit findings, as this is not something we are familiar with.** Proposed change (if any):
212		Comment: **Please confirm if the EMA expect industry to use the definitions in the GvP to identify 'notes' for the PSMF, or the EMA published definitions already published.** Proposed change (if any):
256-265		Comment: **Please ensure these remain in the GvP to safe- guard QAs independence. This wording is much**

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		appreciated! Proposed change (if any):
275-276		Comment: **Please defines management system(s); and organisational system(s).** Proposed change (if any):
279		Comment: **What is the intent of this evaluation? Is the primary purpose process improvement? Please note that some organisations are more hostile than others and requesting customer feedback this may not always be the most objective form of evaluation.** Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<21 September 2012>

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
EuropaBio

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).

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	General comments EuropaBio, the European Association of Biotechnology Industries, thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the 'GVP Module IV – Pharmacovigilance audits'. In general, we support the comments made by EFPIA (European Federation of Pharmaceutical Industries and Associations) to this public consultation. We fully support the development of strong internal audit capability underpinned by proper regulatory oversight to ensure continuing regulatory compliance of an established pharmacovigilance system. However, we would like to highlight that the key objective of the module should be to support companies in performing internal audits, which are complementing national authorities' inspection activities. Against this background, we believe it is important to determine the level of disclosure of internal pharmacovigilance audit documents to regulators and the public. Internal audits or self inspections are conducted by the marketing authorisation holders in order to monitor the implementation and compliance with good pharmacovigilance practice principles and to propose necessary corrective actions and to inform process improvements. Such audits are conducted in an independent and detailed way by designated internal or external auditors. Ordinarily, given the nature of such internal audits, and the need to ensure mutual confidence and openness on a cross-functional basis within the organisation, in practice, such internal audit reports are not routinely disclosed to authorities. Company internal audits cannot substitute for authority inspections. They are designed to constantly optimize company processes in terms of compliance. The frequency of audits consequently is much higher than inspections. Any finding will be followed-up with corrective actions. Once these are remedied they will not be of relevance for an authority inspection anymore nor will they provide useful information to the public. Consequently line 333 – 340 states: "The marketing authorisation holder shall place a note concerning the main audit findings* and audit 333 recommendations, including critical and major audit findings/audit recommendations of any audit 334 relating to the pharmacovigilance system in the pharmacovigilance system master file (PSMF). Based 335 on the audit findings*and audit recommendations, the marketing authorisation holder shall ensure that 336 an

Stakeholder number *(To be completed by the Agency)*	General comment
	appropriate plan detailing corrective and preventative action is prepared and implemented. Once 337 the corrective and preventative actions have been fully implemented, the note may be removed [DIR 338 Art 104(2), IR Art 13(2)]. Objective evidence is required in order that any note of audit findings can be 339 removed from the pharmacovigilance system master file (see Module II). As such we assume the respective sections of the PSMF will not be made available to public and we would welcome an opportunity to discuss with the EMA the circumstances in which certain information derived from internal audits could be properly disclosed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 August 2012

Submission of comments on 'good pharmacovigilance practices Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
European Organisation for Rare Diseases (Eurordis)

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*).*

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

1. General comments

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

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')*
133		Comment: among major structural changes, not only mergers but also acquisitions should be mentioned explicitly. When merging, the management of both companies usually benchmark their respective Standard Operating Procedures and adopt the better one. For an acquisition, the SOPs of the acquiring company are imposed to the acquired company, not necessarily after comparison and benchmarking. Proposed change: - mergers, acquisitions, major re-organisation or other re-structuring of the pharmacovigilance system, (specifically for marketing authorisation holders, this may lead to a significant increase in the number of products for which the system is used);
130-145		Comment: another important structural change, both for marketing authorisation holders, Member States and EMA, is the accession of a new Member State in the EU. Currently one acceding country (Croatia), candidate countries (Former Yugoslav Republic of Macedonia, Iceland, Montenegro, Serbia, Turkey) and potential candidates (Albania, Bosnia and Herzegovina, Kosovo under UN Security Council Resolution 1244) are very heterogeneous and some of their public health systems present challenges.
299-305		Comment: in case of co-marketing of a medicine in the EU, the pharmacovigilance system of each company should not be audited separately as the quality and efficiency of the monitoring of the active substance should be the same in all Member States. Proposed change: The marketing authorisation holder in the EU is required to perform regular risk-based audit(s) of their pharmacovigilance system [DIR Art 104(2)], including audit(s) of its quality system to ensure that the quality system complies with the quality system requirements [IR Art 8,10,11,12,13(1)]. The dates and results of audits and follow-up audits shall be documented [IR Art 13(2)].

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		In case of co-marketing, or when an active substance is marketed by different marketing authorisation holders, the pharmacovigilance audits should be conducted simultaneously and in a coordinated manner by the auditors. See IV.C.2. for further details of the requirements for audit reporting by the marketing authorisation holder to competent authorities and the Agency.
332-343		Comment: it could be interesting to discuss the reports of the audits of marketing authorisation holders of products of the same class, or of products based on the same active substance at a public hearing under the auspices of the PRAC. Proposed Change: The marketing authorisation holder shall place a note concerning the main audit findings* and audit recommendations, including critical and major audit findings/audit recommendations of any audit relating to the pharmacovigilance system in the pharmacovigilance system master file (PSMF). Based on the audit findings*and audit recommendations, the marketing authorisation holder shall ensure that an appropriate plan detailing corrective and preventative action is prepared and implemented. Once the corrective and preventative actions have been fully implemented, the note may be removed [DIR Art 104(2), IR Art 13(2)]. Objective evidence is required in order that any note of audit findings can be removed from the pharmacovigilance system master file (see Module II). The marketing authorisation holders should ensure that they comply with reporting commitments in line with the legislation, GVP guidance and their internal reporting policies. The dates and results of audits and follow-up audits shall be documented [IR Art 13(2)]. Audit reports for MAH pharmacovigilance systems concerning the same active substance or products belonging to the same class when there is a class issue could be discussed at the occasion of a public hearing called by the PRAC.
344-352		Comment: it could be interesting to discuss the reports of the audits of the Member States and the Agency at a public hearing under the auspices of the PRAC. Proposed change: IV.C.2.2. Reporting by competent authorities in Member States and the Agency Competent authorities in Member States, and the Agency should ensure that they comply with reporting

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		commitments in line with the legislation, GVP guidance and their internal reporting policies. Competent authorities in Member States shall report the results [of their pharmacovigilance system audits] to the Commission on 21 September 2013 at the latest and then every 2 years thereafter [DIR 349 Art 101(2)]. The Agency shall report the results [of its pharmacovigilance system audits] to its Management Board on a 2-yearly basis [REG Art 28f]. The reports to the European Commission will follow an agreed format. Reports could be discussed at the occasion of a public hearing called by the PRAC.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 September 2012

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
Gilead Sciences International Limited

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

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).

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

1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
184-185		Comment: The detailing of the audit programme document is too prescriptive. The audit programme should align with the audit strategy and the audit list in the Pharmacovigilance System Master File (PSMF), thus this is duplication of effort. The details of the audit will be included in the audit plan. Proposed change (if any):
333		Comment: It is understood that the PSMF will contain data relating to major and critical audit findings. This module implies the inclusion of other recommendations, in addition. Proposed change (if any): Please clarify what is meant by the other 'recommendations'.
333-334		Comment: The output of an audit is observations concerning identified non-compliances. It is not the responsibility of the auditor to provide recommendations on how the non-compliance should be addressed. Proposed change (if any): Recommendations to be removed.

Please add more rows if needed.

2012-09-12

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
H.LUNDBECK

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*).*

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

1. General comments

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

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')*
Section IV.B.2.3.2, line 201 + General comment to appropriate sections.		Comment: According to the text, the audit findings and recommendations should be documented in the audit report. Please consider if the auditees/process owners have the full picture and is more appropriate to give recommendations. Additionally please clarify if recommendations are expected per audit finding, or if can be done on an overall audit level, based on major points of attention in the audit. Proposed change (if any):
Line 268 - 277		Comment: As per Module I (I.B.7) it is organisation responsibility to ensure adequate training and qualifications. Please consider to highlight this in the paragraph IV.b.3.1.2. Proposed change (if any):
IV.C.2.1. Line 333-340		Comment: As per Directive 2010/84/EU (Pharmacovigilance; Chapter I, Article 104) states that the marketing authorisation holder shall place a note concerning the main findings of the audits on the PSMF. According to Module IV: "The marketing authorisation holder shall place a note concerning the main audit findings and audit recommendations, including critical and major audit findings/audit recommendations of any audit relating to the pharmacovigilance system in the pharmacovigilance system master file (PSMF). As per Module II (II.B.4.7)

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		The pharmacovigilance system master file shall also contain a note associated with any audit where significant findings are raised. This means that the presence of findings that fulfil the EU criteria for major or critical findings must be indicated (see Module IV). The audit report must be documented within the quality system; in the pharmacovigilance system master file it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s). In the annex, in the list of audits conducted, those associated with unresolved notes in the pharmacovigilance system master file, should be identified. The note and associated corrective and preventative action(s), shall be documented in the pharmacovigilance system master file until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified [DIR Art 104(2)]. The addition, amendment or removal of the notes must therefore be recorded in the logbook. As per Directive notes of main audit findings needs to be kept in PSMF until corrective actions are fully implemented. The Module II states that notes of major and critical findings should be kept in PSMF and according to Module IV notes of main and major and critical findings and audit recommendations should be placed in PSMF. Proposed change (if any): Please re-consider the requirement in Module IV in a light of the Directive 2010/84/EU and consider harmonising the requirement within the GVP Modules.

Please add more rows if needed.

August 30, 2012

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
Netherlands Pharmagovigilance Centre Lareb

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).

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Line 230-231 Please specify *Serious* concerns: Are these based upon *critical* or also *major* audit findings? Line 323-326 How does the common methodology and harmonised planning, implementation and reporting by every Competent Authority take place? Who will have the initiative? How will this be processed? When will this be effective? Line 348-350 *Competent authorities shall report the results of their PV system audits to the Commission on 21 September 2013 at the latest and every 2 years thereafter:* bearing in mind the strategic level audit planning is in 3-5 years cycles, only part of the PV audits will have been performed after every 2 years; the 2-year period is too short to cover all PV issues for auditing. A solution would be to have the competent authorities report only every 3-5 years to the Commission. Alternatively, if reporting has to take place every 2 years, please specify in the Guideline that this concerns only results of part of the PV audit cycle.

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21st September 2012

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
Medicines and Healthcare products Regulatory Agency (MHRA) – GPvP Inspectorate

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).

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	There is no reference in GVP module IV to maintaining a list of all scheduled and completed audits in the annex to the pharmacovigilance system master file, as per IR Article 3 (5) and GVP module II.B.4.8. This could be added to section IV.B.2.2. Tactical level audit planning.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 72		Comment: Missing word. Proposed change (if any): approach pharmacovigilance audits.
Line 79		Comment: Change 'and' to 'an'. Proposed change (if any): provides an outline of the operation of the EU network in respect of pharmacovigilance audits.
Line 113		Comment: The auditor(s) may not always be responsible for performing risk assessments in relation to the planning of audit activity, especially in small organisations. Proposed change (if any): In order to implement a risk-based approach to pharmacovigilance audits, the auditors should carry out and document risk assessments as a basis for the strategic, tactical and operational planning of pharmacovigilance audit activity in their organisation.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 113-115		Comment: Is it necessary to mandate that the risk assessments are documented? Is it sufficient for the MAH to document their risk-based approach as part of their strategic level planning, and document their audit programme as the output from this planning? Proposed change (if any): …should carry out and document risk assessments as a basis for the strategic, tactical and operational planning of pharmacovigilance audit activity in their organisation.
Line 118-171		Comment: Is it the intention that the MAH documents their high level statement of strategic audit planning in the pharmacovigilance system master file, including how the audit activities will be delivered over a period of time, their list of all possible audits that could be performed, and their assessment of risk, resources and training needs? If so, section IV.B.2.1 on strategic level audit planning should make reference to the pharmacovigilance system master file and GVP module II. Proposed change (if any):
Line 152		Comment: Missing word. Proposed change (if any): pharmacovigilance activities that are being performed by affiliate or third party…
Line 174		Comment: Why does the plan need to be approved by the head of the organisation? I think it would be better to refer to management as per line 202. Proposed change (if any):
Line 212-231		Comment: Proposed changes to the grading definitions. Proposed change (if any): ● **critical** is a fundamental weakness in one or more pharmacovigilance processes or practices that adversely

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		affects the whole pharmacovigilance system and/or the rights, safety or well-being of patients, or that poses a potential risk to public health and/or represents a serious violation of applicable legislation and guidelines. The audit recommendation aims at introducing mitigating action that addresses the risk of the critical audit finding so that it is not detrimental at the level assessed anymore; Immediate action is required; • **major** is a significant weakness in one or more pharmacovigilance processes or practices, or a fundamental weakness in part of one or more pharmacovigilance processes or practices that is detrimental to the whole process and/or could potentially adversely affect the rights, safety or well-being of patients and/or could potentially pose a risk to public health and/or represents a violation of applicable legislation and guidelines which is however not considered serious. The audit recommendation aims at introducing mitigating action that addresses the risk of the major audit finding so that it is not detrimental at the level assessed anymore; Prompt action is required; • **minor** is a weakness in the part of one or more pharmacovigilance processes or practices that is not expected to adversely affect the whole pharmacovigilance system or process and/or the rights, safety or well-being of patients. The audit recommendation aims at introducing mitigating action that addresses the risk of the minor audit finding so that it is not detrimental at the level assessed anymore; Action within a reasonable timeframe is required.
Line 233-235		Comment: There should be more emphasis on the preparation of a corrective and preventative action plan, and root cause analysis and impact analysis of identified audit findings, where appropriate. Proposed change (if any): The management of the organisation is responsible for ensuring that the organisation has a mechanism in place to adequately address the audit recommendations arising from pharmacovigilance audits, including the preparation of an action plan.
Line 245		Comment: The title of section IV.B.3 is 'Quality system and record management practices' but there is no further reference to record management in the section. There should be guidance on the retention of audit reports and evidence of completion of actions, or a reference to GVP module I section I.B.10. Record management. Proposed change (if any):

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 277		Comment: This line is confusing; it implies that training of auditors is optional. I think the line can be removed because training is stated on line 271 and the requirements for training of personnel are clearly defined in GVP module I. Proposed change (if any):
Line 341-342 Line 346-347		Comment: I think the following lines are redundant and can be removed: "The marketing authorisation holders should ensure that they comply with reporting commitments in line with the legislation, GVP guidance and their internal reporting policies." "Competent authorities in Member States, and the Agency should ensure that they comply with reporting commitments in line with the legislation, GVP guidance and their internal reporting policies." Proposed change (if any):

Please add more rows if needed.

<21 September 2012>

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from: Novartis

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

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*).*

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Novartis welcome the opportunity to provide comments on this draft GVP module. The module is well structured and therefore our comments are very few and focus on a small number of areas in the text were further clarity could be given. Further details and advice would facilitate the audit process and the work carried out by the auditor, the auditee and any other relevant role directly or indirectly involved (e.g. compliance group, EU QPPV office). In particular, a streamlined guidance on the rationale for timing and scope of audits, on the grading of audit recommendations and on the actions the Agency shall undertake (e.g. which results will be reported) would be very helpful to fully understand the module and apply it accordingly.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 174		Comment: Please can you clarify who represent the "head of the organisation"? Is it the head of Quality Assurance?
184-185		Comment: The description of the plan for each audit appears too detailed at this stage. Proposed change (if any): *description of a high level plan for each group of audits e.g. one for subsidiaries other for license partners etc*
186-187		Comment: The rationale for timing, periodicity and scope should not be based only on the document risk assessment Proposed change (if any): *based on the document risk assessment and also routine audits e.g. the ones every three years*
206-334		Comment: Please clarify if audit recommendations are to be graded. If they are graded how do audit recommendations differ from audit findings?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
230		Comment: Please clarify the terms "urgently" and "expedited". Please also provide guidance on how to manage these timeframes. Similar to the audit findings classification, to avoid confusion please indicate some example of serious concerns that require expedited communication to management.
237-238		Comment: Please clarify how "formally accept the risk of not taking action" should be done.
279-280		Comment: Please provide any guidance/advise on the type of metrics to for the evaluation of the audit.
307-309		Comment: Please provide guidance on the QPPV's involvement (role and responsibilities) in strategic level audit planning and tactical level audit planning.
351-352		Comment: Please clarify which results the Agency shall report (e.g. critical only, critical and major)

<21 September 2012>

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
Pfizer Inc

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
	Overall, this draft module (GVP Module IV – Pharmacovigilance audits) is very comprehensive and provides detailed and helpful guidance on expectations regarding pharmacovigilance audits and inspections. We thank the Agency for efforts to provide comprehensive guidance. Further, we appreciate the opportunity to review this document and provide the following comments with the goal of improving, and thereby strengthening, the final guidance.
	We reference the extensive comments made by the European Federation of Pharmaceutical Industry Associations (EFPIA), which we fully endorse, and we also offer the following additional suggestions to improve the Guideline. We would be glad to respond to any questions the Agency may have regarding our comments.
	In common with other GVP modules, this module provides clarification as to the meaning of the words "shall" and "should" (lines 63-65). It is important to set expectations, as auditors and inspectors must have a clear understanding in this regard. However, this guideline, in general, is unnecessarily prescriptive regarding the strategy, planning, and execution of audits. Three levels of planning (strategic, tactical, and operational) seem to be required with accompanying documentation. In contrast, certain terms are vague. For example, certain modifiers and imprecise references to time are used throughout the document. Terms such as may, can be, periodic basis, and regular basis do not clarify expectations. Several of these terms, processes, and timeframes could be clarified or supported by examples. Perhaps minimum requirements would be more transparent and not open to variation in interpretation. See specific comments, below.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 92		**Comment**: The term "statement" is vague and otherwise lacks definition. **Proposed change**: Modify line 92 to read "... records, ***written*** statements, or other ***documents*** ~~information~~ ***from durable sources***, which are relevant...."
Line 98		**Comment**: The meaning of "high-risk areas" is not clear. Further, it is not clear whether the intent of using the term "high-risk areas" is meant to refer to aspects of the system that could be subject to major findings or either major or critical findings. As the draft is written, there is an implication that there are always areas of "high" risk. In reality, the goal of most organizations is to simply determine what the levels of risk are in various areas, all of which may be low. **Proposed change**: Revise line 98 to read "…to determine the high-risk areas***, if any,*** where risk…"
Line 113-116		**Comment**: In larger organisations, the risk assessment, strategic audit functions, and often the tactical planning of audits would likely best be performed by audit management rather than the auditors themselves. Further, the types of audits covered under this guidance are unclear, i.e., study sites, local affiliates, vendors, etc. **Proposed change**: Modify line 113 to read " .....pharmacovigilance audits, the auditors ***or audit management,*** should carry out ..."
Line 119		**Comment**: It is not clear whether the expectation is a list of all possible systems or entities that could be audited with considerations for emerging risks and risk assessments of all entities, or all possible audits that will be performed, or otherwise. This is unnecessarily prescriptive. Listing all possible audits and areas of risk for a 3- to 5-year cycle would not be an efficient use of resource as this would change over time due to changes in

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		processes and organizations, etc. An audit strategy covering a 3- to 5-year period is an extended timeframe that encompasses a high-degree of uncertainty, considering the ever-changing and modulating nature of business alliances/partnering and related pharmacovigilance responsibilities. However, there may be certain types of audits routinely planned on a 3 or 4 year cycle, such as audits of major affiliates of a global company. These latter audits would ordinarily be mentioned in an SOP, not in a formal audit plan that spans 3- to 5-years. **Proposed change**: (a) Modify line 119 to read "…over a period of time, longer than the annual programme, usually for a period of ***~~3-5 years~~ 2 years or more.*"** (b) Modify line 120 to read ".....audits that could be ***reasonably*** performed and an assessment of risk ....."
Line 128-129		**Comment**: Is this section intended to reference CROs/vendors that are contracted to perform PV functions for sponsor is identified in the audit strategy? **Proposed change**: Modify line 129 to read "...MAH affiliates or third parties, ***such as contract organisations and other vendors.***"
Line 173-174		**Comment**: Requires that the audit program be 'approved' by the head of the organization. Please clarify which head of the organization this is referring to i.e. head of MAH/company, head of quality assurance, head of PV organization, etc. How does the agency expect this to be documented. Suggest clarifying **Proposed change**: Modify line 174 to read "...should be approved by ***~~the head of~~ a designated individual within*** the organisation ***who is responsible for the pharmacovigilance audit program***."
Line 181		**Comment**: The intended meaning of "insufficient past audit coverage" is not clear. It would also be helpful to have a definition and/or 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')*
		Proposed change: Modify line 181 to read "...take into account ***historical ~~areas with insufficient past~~*** audit coverage, ..."
Line 184		**Comment**: Reference to annual audit programme: "... should include a brief description of the plan for each audit to be delivered, including its scope and objectives." Other than the title of the entity, it is not necessary to prospectively map out this level of detail. Rather, the risk assessments identify areas of risk; once planning begins the scope is further defined. In addition, the audit programme document should include those entities whose risk assessment resulted in inclusion in the plan to audit, but should not impose the administrative burden of including those entities that were assessed but not scheduled for audit. **Proposed change**: Revise line 184-185 to read " ... audit programme document should ***identify the entity to be audited and define the aligned risk. The intent of the risk-based approach is to focus on areas of greatest risk to the organisation's pharmacovigilance system, thus, entities assessed for risk but not scheduled for audit due to low risk need not necessarily be included in the auditi programme document. ~~include a brief description of the plan for each audit to be delivered, including its scope and objectives.~~***"
Line 128-129		**Comment**: Is this section intended to reference CROs/vendors that are contracted to perform PV functions for sponsor is identified in the audit strategy? **Proposed change**: Modify line 129 to read "...MAH affiliates or third parties, ***such as contract organisations and other vendors.***"
Line 188		**Comment**: The term "regular intervals" is not defined and suggests that deviation from a set interval would be

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		discouraged, even in situations where more frequent audits would be indicated based on results of risk assessment. **Proposed change**: Modify line 188 to read "... pharmacovigilance audit(s) should be ***performed ~~at regular intervals~~ when indicated by risk-based sampling*** to assure that the system complies ..."
Lines 212 - 229		**Comment**: A specific ~~grading~~ **classification of findings** is proposed that will be specific to ~~PV~~ **pharmacovigilance** findings. It is suggested ~~to provide~~ **that the agency provide** concrete examples for each category~~,~~ to promote standardization. This could be applied not only ~~for~~ **to** audits but also ~~for~~ **to regulatory** inspections. The terms "immediate" (line 217), "prompt" (line 224), "reasonable" (line 229), "urgently" (line 230), and "expedited" (line 230) are vague and do not convey clear expectations regarding timelines or distinctions as to their intended meaning. **Proposed change**: (a) Revise lines 212-229 to provide examples for each category: Critical, Major, and Minor findings. (b) Insert a new paragraph after line 231: "***Actions referenced in this section of the guideline, i.e., immediate action, prompt action, action within a reasonable timeframe, concerns that need to be urgently addressed, or communicated in an expedited manner, are intended to convey timelines that are appropriate, relevant, and in line with the relative risk to the pharmacovigilance system. The acknowledgement and response to a critical finding, in general, should be faster than to a minor finding, even though complete mitigation or resolution of the finding may not be completed in the same timeframe. The precise timeframe for action(s) related to a given critical finding, for example, may differ depending on the planned action(s).*** "
Line 365-402		**Comment**: The glossary for this module is very useful; it is recognised that the information it contains will be incorporated into GVP Annex I (Definitions) and the current glossary will be sunset in the revised module. However, it is important to ensure consistency not only within a given module, but also across the various GVP modules to facilitate practical aspects of implementation.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Ensure that all terms, definitions, and acronyms/initialisms are accurately added to GVP Annex I (Definitions), as planned, and are used consistently within each module and across all modules.

Please add more rows if needed.

21 September 2012

Submission of comments on 'GVP Module IV – Pharmacovigilance audits' (EMA/228028/2012)

Comments from:

Name of organisation or individual
PHARMIG

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).

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	PHARMIG, the association of the Austrian pharmaceutical industry, would like to thank for the opportunity to comment on GVP Module IV – Pharmacovigilance audits.

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')*
218		Reference: Major Comment: In module III, line 530, a significant major finding is mentioned; please add a definition of “significant” here Proposed change (if any):
388		Reference: IIA International Standards for the Professional Practice of Internal Auditing4 Comment: Proposed change (if any): IIA International Standards for the Professional Practice of Internal Auditing3
		Comment: Proposed change (if any):

Please add more rows if needed.