25 June 2012
EMA/428811/2012
Patient Health Protection

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

GVP Module I – Pharmacovigilance systems and their quality systems

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

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

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

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

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An agency of the European Union

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
Association of Clinical Research Professionals (ACRP)

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The reference check of the document is difficult, as reference to specific Articles of the draft Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC is provided in square brackets with the indication “IM”, but the according regulation document is not available on the internet.

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 118-125		Comment: We would like to suggest re-considering the order of the bullet points. Preventing harm from adverse reactions to humans (bullet 2) and protection of patients' health (bullet 4) should surpass compliance with the legal requirements for pharmacovigilance tasks (bullet 1). Proposed change (if any):revise order as follows: first = bullet 2, second = bullet 4, third = bullet 3, forth = bullet 1
Line 455		Comment: The link is not directing easily to the referenced document. Proposed change (if any): Please replace the link by: http://ec.europa.eu/health/files/eudralex/vol-2/c17_1/c17_1_en.pdf
Lines 585-586		Comment: This quality system process should be the same as for competent authorities and the Agency (lines 801-803). Proposed change (if any): This bullet should read: monitoring and validating the use of terminology, either systematically or by regular random evaluation, with data entry staff being instructed in the use of terminology and their proficiency verified
Line 769		Comment: The link is not directing to the according document. We assume that the link will be provided once the planned 1st meeting of the PRAC has been held in July 2012 (according to the presentation (The PRAC – Pharmacovigilance Risk Assessment Committee, Workshop, 17 June 2011, London Dolores Montero, AEMPS & Roberto De Lisa, European Medicines Agency). Proposed change (if any):

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
120-121		Please define occupational exposure. Would it include health care professionals/pharmaceutical industry workers...? Would a person with occupational exposure be considered the same as a patient? The term occupational exposure appears in some instances along the document (such as line 224), but not consistently.
132-133		These sentences can be confusing since not all persons are directly involved to pharmacovigilance. Proposed change: All persons within the organisation should receive training on adverse event reporting and should support the pharmacovigilance system and its quality improvement in a degree according to their tasks and responsibility.
176		Proposed change: I.B.7. Training of personnel for pharmacovigilance within the company
176-198		Proposed change: This section could be subdivided in two sections: one section for employees directly involved in pharmacovigilance activities (177-193), and another section for staff in other areas (194-198).
190-192		These sentences might be interpreted as if an exam should be undertaken for every task. Proposed change: There should be a process in place within the organisation to check that all employees have been trained at the appropriate level and in line with agreed professional development plans. In addition, for those tasks that are considered to be critical, there should be a process to check the employee´s understanding and conduct of pharmacovigilance activities.
193 - 197		This paragraph mentioned that an *adequate training* for these areas: Clinical trials Technical products complaints Medical information Sales and Marketing Regulatory Affairs Legal Affairs 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 (if any): It will be very useful for Pharmaceutical Industry to specify in more detail what is considered an “adequate training” for these areas.
216-221 & 743-744		The text in lines 217-221 “marketing authorisation holder shall follow-up such information...including information...published in medical literature” seems to contradict that of lines 742-743 (Specific pharmacovigilance tasks of the Agency include): monitoring selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances.
254-257		This line could be misinterpreted as that all documents should be retained. Proposed change: As part of the quality system, a record management system shall be maintained, describing all documents used for pharmacovigilance activities, describing the management for each record category, ensuring their retrievability as well as traceability...
338-344		How competent authorities will keep accessible the organizational structures or some regarding transparency of processes? Would it be possible to add the details be added to this section? For example how/when periodic safety reports/ ICSRs are reviewed.
438-439: A description of the pharmacovigilance system shall be developed by the applicant for a marketing authorisation in the format of a pharmacovigilance system master file (PSMF) and be maintained by the marketing authorisation holder after the marketing		Comment: Please advise how to proceed when different MAHs are being declared in advance in the registration dossier. We understand that each MAH should present their own PSMF and should answer any comment or query that the Agencies would have. Regarding the description of pharmacovigilance system, please confirm if we find in the case where the applicant supplies of a Common Technica Document (CTD) for differnt MAHs in different countries. Which PSMF should be included. The one from the applicant and all the MAHs. Who will then act as EU-QPPV? Proposed change (if any): When different marketing authorisation holders are declared in the same registration by the applicant, all PSMR for each MAH and product should be presented. Each MAH will be responsible for developing and maintaining their own systems.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
authorisation has been granted		
360		What is it meant by quality defect systems? It does mean product complaints? Further clarification needed on this point.
[364]: Communication information to patients and healthcare professionals about changes to the risk-benefit balance of products for the aim of safety and effective use of medicinal products:		Comment**:** Please clarify how MAH should make these kind of communications, (after approval of the Agency, which formats, etc)
373		Typo: pharmacovgilance
584-585		Could you please clarify what it is meant by “proficiency verified”? Will an exam be necessary or simply a training record?
587-589: the retention		Comment: Please see 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')*
of essential documents describing the pharmacovigilance system as long as the system described in the pharmacovigilance system master file (PSMF) exists and for at least further 5 years after it has ceased to exist		Proposed change (if any): the retention of essential documents ***(both paper or electronic documents)*** describing the pharmacovigilance system as long as the system described in the pharmacovigilance system master file (PSMF) exists and for at least further 5 years after it has ceased to exist. Please clarify if a an electronic validated scanned copy could substitute original paper format.
601-602 Documents can be retained in electronic format, provided that the electronic system has been appropriately validated. and appropriate arrangements exist for system security […]		Comment: How can we assure validation of information technology program? Please specify how this validation for electronic documentation retained should be done. Does a marketed electronic program suite (eg. Microsoft Office suite) has to be validated? Proposed change (if any): Mention of an appropiate validation of an electronic format would be adequate

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
624-626		Could you please rephrase to clarify the following points?: - -Will all (global or local) contracts that include pharmacovigilance activities need to be included? Is it enough to include a list and description of contracts?
638-644		Could you please give some examples regarding duplicates? Proposed change (if any):
643-645: Article 82(1) of Regulation (EC) No 642 726/2004 states that the use of two or more commercial designs for a given medicinal product covered by a single marketing authorisation is not prohibited by the Regulation. Such products are called duplicates.		Comment: Please clarify this statement. In which cases this is applying? Different indications? Different dosage forms? Does it refer to 'change of ownership' applications?
808-812		We suggest adding also the information to the marketing authorisation holder. Proposed change: (...) healt, competent authorities in Member States and the Agency inform each other, the European Commission and the Marketing Authorisation Holder not less than 24 hours prior to public ..
850-853: A competent		Comment: If so, it would be suggestable to make public to all affected stakeholders which part (or all) of 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')*
authority in a Member State may transfer any or all of the pharmacovigilance tasks to another organisation, but the ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system always remains withthe competent authority in a Member State.		pharmacovigilance is transferred to another organisation.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
AESGP

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	It is agreed that there should be a quality system for pharmacovigilance. As discussed during the fourth EMA stakeholder meeting on Pharmacovigilance, there is consensus around the fact that each company independently of its size should have a quality system in place for pharmacovigilance. However the requirements should be scalable to various size of companies and proportionate to the risk of medicines placed on the market by the MAH. The administrative burden on the companies should not be larger than the expected benefit for public health otherwise we fear that too high level requirements may be detrimental to core pharmacovigilance activities for small companies. An example of excessive requirements may be found in section I.B.11 : *"All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records."* For smaller companies acting mainly on a national level and having products with a low and well known risk, such requirements can hardly be fulfilled. The "Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC" (EC IM) is often referred to in draft Guideline on good pharmacovigilance practices (GVP) Module I - Pharmacovigilance Systems and their quality systems. Given that the EC IM are not yet finalised and that the final version is not expected to be published before May-June 2012, this makes the commenting on this draft module more difficult.
	No information on any transitional period is provided. We make the plea that a six-month transition period apply after 02 July 2012 to allow for review/update of quality systems already in place in accordance with the requirements laid out in the GVP module I.

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')*
349-375 Major		Comment and proposed change: This is an exhaustive list of Pharmacovigilance processes all considered equally critical. In line with our general comments, this list should be limited to the crucial points, which require appropriate requirements. Some of the points are formulated too generally and are not critical to our mind: - Lines 364-365: communicating information to patients and healthcare professionals about changes to the risk-benefit balance of products for the aim of safe and effective use of medicinal products. This should be limited to significant or clinical relevant changes of the risk- benefit balance. - Lines 359-360: meeting commitments and responding to requests from competent authorities, including provision of correct and complete information. These procedures are sufficiently controlled in separate processes (e.g. regulatory affairs) and do not require separate instructions in the pharmacovigilance system.
502- 504		Comment: It is stated that “when a marketing authorisation holder intends to expand its product portfolio, for example, by acquisition of another company or by purchasing individual products from another marketing authorisation holder, the QPPV should be notified early in the due diligence process in order”: This is not always possible due to confidentiality issues. Proposed change: please add: ‘to the extent possible’
533-534		Comment: It is agreed that a back-up procedure should be in place in case of the absence of the QPPV. The organisation of a back-up procedure might be diverse and would depends on the size and the structure of a company. Proposed change: We would like to propose the following wording in line with GVP module II lines 253-254: “Back-up procedures in the case of absence of the QPPV should be in place , and principles accessible through the PSMF.”

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
117-125		Comment: We suggest changing the order of importance – safety should be before legal requirements. Proposed change: - preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; - complying with the legal requirements for pharmacovigilance tasks and responsibilities;
155		Comment: For clarity change managerial staff to management – throughout the document Proposed change: management should be responsible for:
222		Comment: Insert “to” before patients Proposed change : all information on the risks of medicinal products as regards to patients’ or public health, including
293		Comment: the term “quality objectives” appears 3 times in one sentence Proposed change : rewrite
585		Comment: add “the before this sentence Proposed change: the monitoring of the use of terminology, with data entry staff being instructed in the use of terminology
618		Comment: add “to ensure” to this sentence Proposed change: holder to another organisation, the marketing authorisation holder shall retain responsibility to ensure that …
625		Comment: add ”the” Proposed change: included in the pharmacovigilance system master file (PSMF) [IM Art 4(1)(f)] and a list of the contractual

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
800		Comment: remove “for” from the end of the sentence Proposed change: and the Agency shall put in place the following additional specific quality system processes:…

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 APR 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
ALEXION Europe SAS

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 198: I.B.8. Facilities and equipment for Pharmacovigilance		Comment: In this section which appears to be derived from GMPs, it may be quite difficult to determine what is referred to as “facilities” and “equipment”. Although Alexion acknowledges that quality tools are safe tools to guaranty Pharmacovigilance system efficiency, there should be in this section some example illustrating what is meant and what are the targeted “facilities” and “equipment”. As indeed Pharmacovigilance activities are not performed in a Plant nor in an IT room, this would help Pharmacovigilance staff responsible for and involved in PV system management to set up appropriate processes in this frame. Proposed change (if any):
Line 395 to 397 in I.B.12 section: “monitoring of the performance and effectiveness of the Pharmacovigilance system and its quality system.		Comment: According to the title of that section, audits to be performed should be primarily targeted at examining the Pharmacovigilance system and not the quality system. The wording of sentence line 397 is confusing and may create uncertainty so as to what is aimed at here which is not the audit of the company quality system per se. Alexion thinks that this should also be addressed in future regulation on Implementing measures. It Is propose to rephrase this the other way round as follows: Proposed change (if any): “Risk-based audits of the Pharmacovigilance system shall be performed at regular intervals to assure that it complies with the established quality requirements and to determine its effectiveness [IM Art 16(1), 397 Art 21(1)]. Audits of the Pharmacovigilance system should include audit of its quality system.
Line 466-467		Comment: to be accurate and consistent with other similar wording in this module the sentence : “The marketing authorisation holder shall ensure that the QPPV has sufficient authority to influence the performance of the Pharmacovigilance activities and the quality system” should read: Proposed change (if any): “The marketing authorisation holder shall ensure that the QPPV has sufficient authority to influence the performance of the Pharmacovigilance activities and <u>its</u> quality system”
Line 501		Comment: The current module should also include a sentence possibly at that level (or at the level of line 628), to strengthen the Marketing Authorisation Holder responsibility in informing beforehand the QPPV about any new partnership, outside of the context of a delegation of Pharmacovigilance tasks, that may include

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Pharmacovigilance activities and subsequent responsibilities for this Marketing Authorisation Holder and the QPPV so that it can be ensured that agreements include all necessary provisions. A reference to section I.C.1.5. should be made. Proposed change (if any): “When a Marketing Authorisation Holder intends to establish a partnership with another Marketing Authorisation Holder that has a direct or indirect link with its Pharmacovigilance system, the QPPV should be informed early enough and be involved in the preparation of the corresponding agreement so that all necessary provision relevant to the Pharmacovigilance system are included”.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17th April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
AstraZeneca

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	AstraZeneca welcomes the opportunity to provide feedback to GVP Module I – Pharmacovigilance systems and their quality systems (EMA/541760/2011) AstraZeneca has had the opportunity to contribute to the EfPIA comments and agree to those. Additionally, AstraZeneca would like to provide some further comments which follows below as general and specific comments.
	There is an apparent anomaly as regards QPPV signatures. At present, it is only required for PASS protocols, but not for the Pharmacovigilance System Master File, Summary of Pharmacovigilance System, PSURs or Risk Management Plans. This anomaly needs resolution, to reflect the importance of the QPPV in the pharmacovigilance process. The QPPV should sign off the PSMF and the Summary of Pharmacovigilance System, but signatures can be delegated to others for PSURs, RMPs and PASS protocols.

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 133 - 134		**Comment:** The sentence: “All persons within the organisation should be involved in and support the Pharmacovigilance system on the basis of task ownership and responsibility”, is confusing since not all employees have tasks related to Pharmacovigilance”. **Proposed change (if any):** All persons within the organisation should be trained in forwarding suspected ADRs which they become aware of to their local affiliate.
Line 326		**Comment:** It is unclear what is meant by "their resource management", could cover employees, budget or both. **Proposed change (if any):** ...marketing authorisation holders shall document: their organisational structure related to pharmacovigilance activities.

Please add more rows if needed.

NOTE A L'AGENCE EUROPEENNE DES MEDICAMENTS

OBJET : Position des autorités françaises sur les modules de bonnes pratiques de pharmacovigilance (« Good pharmacovigilance practice modules ») soumis à la consultation publique par l'Agence européenne des médicaments.

Les autorités françaises accueillent favorablement les sept modules des bonnes pratiques de pharmacovigilance européenne qui ont été soumis à la consultation des Etats membres, le 22 février 2012.

Ces projets de texte n'appellent aucun commentaire particulier de la part de la délégation française à l'exception du module VIII – « Post autorisation safety studies ».

Les propositions de modification du module VIII portent sur :
- la page 5/25 après la ligne 129, les autorités françaises souhaitent ajouter "les études PASS peuvent avoir pour objectif de comparer le profil de sécurité d'un médicament à celui d'un comparateur pertinent" ;
- la page 5 /25 ligne 145, les autorités françaises proposent de remplacer "(ISPE GPP, Revision 2, 2007)" par "(ISPE GPP, current version)" ;
- la page 11/25 ligne 375 après « submit », les autorités françaises proposent d'ajouter les mots "the analytical dataset and".

<Date of submission>

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
British Association for Quality Assurance (BARQA)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The deadline to implement this module (July 2012) is too short as some new processes need to be developed and implemented and many processes will need to be updated. This comment is applicable to all modules Proposal: As a transition measure - create an implementation plan with fixed deadlines by July 2012. Implementation to be completed by July 2013. Ensure that during this transition period the regulatory inspectors evaluate the plans and implementation of the plan against deadlines. This proposal is proposed for all
	Comment: reference is made to other modules not currently available this makes it difficult to review completely without the additional information. Proposed change (if any):

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 133-134		Comment: Does this mean the Pharmacovigilance organisation or the entire organisation Proposed change (if any): The Pharmacovigilance organisation should be specifically referenced here. Text should read “All persons within the pharmacovigilance organisation…”
172		Comment: “Motivating all staff members, based on shared values…” This level of detail is inappropriate in this type of guidance. Definitions of motivation and how to motivate staff is very subjective and the guidance should be much more objective and focus on activities that will ensure staff members comply with internal processes and legislation to ensure patient safety. Proposed change (if any): remove lines 172 -173
396		Comment: “risk-based audits of the quality system itself shall be performed at regular intervals”. If a risk based approach is to be used for auditing then also stipulating a regular interval contradicts this. Taking a risk-based approach means you would not necessarily follow a regular interval, as you would focus attention where the biggest risk occurs and so each year the area of focus may change. Proposed change (if any): removal of “at regular intervals”.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
400		Comment: reference is made to module IV, this is not currently available it would have been good to have this released so this section could be reviewed alongside this module Proposed change (if any):
590-592		Comment: Are audit reports and CAPAs considered to be pharmacovigilance data?
98-99		Comment: Although I did not check how it is worded in ISO, the definition provided for Quality Control is misleading as it could be understood that Quality Control is the actual conduct of an activity in line with SOP requirements. Proposed change (if any): Activities focussing on verifying that quality objectives are met as a result of conducting given tasks or responsibilities are called quality control.
112		Comment: Same as lines 98-99, the definition of Quality Control appears misleading. Proposed change (if any):
155		Comment: The module refers to “managerial staff” in several places but it not clear who this might be. Proposed change (if any): Should these responsibilities be assigned to QP or MAH ?
170		Comment: Like for line 155, the module refers to “higher management” in several places but it not clear who this might

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		be. Proposed change (if any): Should these responsibilities be assigned to QP or MAH ?
213		Comment: The concept of “Compliance management” is not clear. Does this refer to the maintenance of compliance metrics ? If not, this section would appear redundant with the need to have SOPs in place to cover specific processes, as specified in I.B.11.3. Proposed change (if any):
350 & 356		Comment: It is not clear what difference exists between those two lines, i.e. “continuous safety profile monitoring and benefit-risk evaluation of authorised medicinal products” and “detection, investigation and evaluation of signals”. Proposed change (if any):
450 to 453		Comment: This paragraph concerns the notification of the QPPV contact details to Competent Authorities. It is however not clear which department of the Competent Authorities should be notified and whether notification though Marketing Applications and Variations is sufficient. This already caused some confusion with Vol.9A whereby the MHRA expected the inspectorate to receive EU QPPV contact details. Proposed change (if any):
461		Comment: The wording suggests that a QPPV may work for several PV Systems only if it is for the same MAH, which would more or less exclude the use of contract QPPVs and seems contrary to previous text in the same

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		paragraph (lines 459-460) stating that “A QPPV may be employed by more than one MAH”. Proposed change (if any):
492-493		Comment: “The managerial staff should provide the QPPV with a copy of the corrective and preventive action plan following each audit”. Does this apply to audits conducted within the EEA only, or world-wide ? Proposed change (if any):
593-597		Comment: Until now, the Authorities would contact the MAH and request changes to Product Information. This suggests that the MAH is now required to access the EMA website for updates. This does not appear appropriate as all MAHs would have to scan information when only a small percentage will be relevant to them. In addition, the requirement could be made more specific in terms of frequency and records keeping to demonstrate compliance with such a requirement. Proposed change (if any):
403 and 408		Comment: Not all companies perform specific “follow up audits” as resolution of observations is captured in the final audit report. The implementation of the previous commitments are then reviewed when the system is audited as part of the audit schedule. Therefore remove “follow-up audit” Proposed change (if any): a report shall be made of the results of each quality audit and any responses are reviewed by the management responsible for the matters audited
465-466		Comment: Please clarify if this is required where the EU QPPV resides with the MAH and the National QPPV is a business partner, such as a Distributor or Marketing Partner.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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):
639-645		Comment: It would appear relevant to conduct pharmacovigilance on the basis of complete worldwide data sets for all types of MAs, and not only for centrally authorised products, as suggested here. **Proposed change (if any):**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 April 2012

Submission of comments on 'Guideline on Good Pharmacovigilance Practices: Module I – Pharmacovigilance Systems and their Quality Systems' (EMA/541760/2011)

Comments from:

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

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	Comment: The multiple levels of hierarchy suggested in the QMS are onerous and overly complicated for SMEs, where a more simplified quality system is in place. The QMS should be allowed to grow organically with the company and should be appropriate/proportionate to the company and risks involved.

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')*
85 (also line 332)		Comment: This infers that the guidance is only relevant to authorised products but Pharmacovigilance (PV) obligation starts at submission.
104		Comment: We presume this means that details of the quality system need to appear in the PV system.
133		Comment: Is this saying that everyone in an organisation e.g. MAH, needs to be involved in PV? Does this just mean basic PV training or more?
146		Comment: We are unclear who 'all persons' are here e.g. QA or PV staff?
157		Comment: 'adequately controlled and clearly documented' is open to interpretation.
161		Comment: Review at 'regular intervals' is open to interpretation.
169 (also 396)		Comment: Frequency of audits is open to interpretation.
181 (also 347, 370-375)		Comment: 'Business continuity' might be open to interpretation e.g. is it just the back-up procedures if the QPPV is absent, or more, such a disaster management etc.? More details are provided in 370-375.
193		Comment: Are professional development plans a requirement? For small companies this can be quite a resource-intensive requirement.
194		Comment: How will 'adequate training' be defined?
200-211		Comment: We don't find the wording of this ('facilities and equipment') flows that well, as it seems a bit 'GMP' related rather than PV, which is mainly IT based.
246		Comment: How will the CA's 'guarantee independence'?
282-336		Comment: In the case of outsourcing all PV functions we are not totally clear how all this will work e.g. can it all be delegated to the service provider or will the MAH also have to prepare summary data on top of the provider's PV system?
364		Consider inserting 'negative' changes.
391		Comment: 'managerial staff' to monitor the quality system is open to interpretation.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
438		Comment: A template for the PV system would be useful as a starting point.
453-455		Comment: Exactly when variations will still be required for changes to PV system may need exploring/ further explanation.
467 - 473		Comment: What about co-licensing situations - when multiple PV systems come together and are "overseen" by a "lead" QPPV - the "lead" QPPV would not be able to have authority or influence over another MAHs system.
482-483		Comment: Is it sufficient for the QPPV (e.g. a services provider) to have an overview of all contractual arrangements for the MAH's own MAs or do they need to know about all products e.g. OLSs on third party MA's where the PV responsibility belongs to the third party? It is assumed that this refers to contracted-out pharmacovigilance activies. Please confirm this assumption
488		Comment: The frequency of 'periodic basis' for compliance information is open to interpretation.
502-509		
523-525		
528		Comment: What does "a natural person" mean?
553		Comment: What it meant by "all PV-related documents" in relation to the submission? This could be interpreted as very wide ranging, and not just those documents mentioned in GVP.
580-597		Comment: We are unclear why this 'specific quality system' information needs to be presented separately to the main information (I.B.9 and I.B.11)
595		Comment: What does 'continuously' mean in terms of checking EMA for updates? Especially relevant for generic MAs. Consider changing to 'regularly'?
600-602		Comment: Some guidance on appropriate validation of electronic filing systems is required. Is Installation Qualification adequate if a MAH is using basic folder structures on a standard server?
621-628		Comment: In the case of using a PV Services Provider, we are unclear of the expectation: e.g. (a) PV Services Provider prepares PV System master file, MAH prepares summary of master file, adding in local personnel etc. (b) MAH prepares PV System master file and summary, based on that of provider. Does the PV Services Provider have to include the services and contractual arrangements in their master file or will they move to a different master file per MAH to which they provide services? May be clearer in Module

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		II? It is assumed that the requirements may be fulfilled by the MAH or the PV Services Provider, albeit that the MAH must ensure that it takes place
629-638		Comment: Suggests that contracts for PV Services and even more simple Safety Data Exchange Agreements will need to increase significantly in terms of level of detail/ complexity, and be more like SOPs.
644		Comment: Is this correct in terms of CP approved MAs? We had understood that duplicates, with different pack designs, are based on separate MA's not a single one?
686-691		Comment: How will this work if there are different MAHs to the RMS-MAH?
744		Comment: We are looking forward to seeing the list of 'certain' active substances for which EMA will monitor the literature and would ask if there is an estimated date when this will be available?
851		Comment: Does this mean that CA's can delegate their PV system to commercial organisations as well as other CA's? the directive refers to delegation to a member state - not a private entity – can this be confirmed?

Please add more rows if needed.

UK BioIndustry Association

Influencing progress and enabling connections for UK bioscience

European Medicines Agency
7 Westferry Circus
Canary Wharf
London E14 4HB

By email: gvp@ema.europa.eu

18 April 2012

Dear Sirs,

Submission of comments on good pharmacovigilance practice modules

The BioIndustry Association (BIA) welcomes the opportunity to submit these comments on the first batch of modules on good pharmacovigilance practices (GVP) issued for public consultation.

Established in 1989, the BIA is the trade association for innovative healthcare focused bioscience enterprises. BIA members include emerging and more established bioscience companies, pharmaceutical companies, academic research and philanthropic organisations, and service providers to the UK bioscience sector. The BIA represents the interests of its members to a broad section of stakeholders, from government and regulators to patient groups and the media. Our goal is to secure the UK's position as a global hub and as the best location for innovative research and commercialisation, enabling our world-leading research base to deliver healthcare solutions that can truly make a difference to people's lives.

We support the new EU pharmacovigilance legislation which aims at strengthening the Community system and better protecting public health.

The BIA endorses the comments on the GVP modules submitted by EFPIA, the European Federation of Pharmaceutical Industries and Associations.

We look forward to continuing the dialogue with the Agency and EU regulatory authorities to facilitate the implementation of the new pharmacovigilance legislation.

Yours faithfully,

Head of Regulatory Affairs

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

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

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	In this draft Guideline on good pharmacovigilance practices (GVP) Module I - Pharmacovigilance Systems and their quality systems “Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC” is cited which is however not yet finalised. Therefore, the comments can only be preliminary.
	It is agreed that a pharmacovigilance system must be quality assured. However, the requirements and provisions have to be proportional to the risk of the products placed on the market by a marketing authorisation holder. The administrative burden on the companies should not be larger than the expected benefit for public health. As an example the requirements in section I.B.11 can be mentioned. *“All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records.”* These requirements may be appropriate for a global company with a complex structure and with innovative products for which the risks are not known. For smaller companies acting mainly on a national level and having products with a low and well known risk such requirements can hardly be fulfilled.
	Overall a strengthening of the duties of the Marketing Authorization Holder (managerial staff) and the QPPV was noticed and more documentation is needed to be compliant with the Module (e.g. job descriptions for managerial and supervisory staff, definition of key performance indicators).

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 78 - 80		**Comment**: The difference between the modal verb for the legal requirements „shall" and the modal verb for the implementation of legal requirements "should" is not really clear and thus clarification is needed.
Line 153 - 155		**Comment**: We are wondering that the "managerial staff" is rather responsible for the quality system than the "QPPV"? Furthermore a definition for "managerial staff" is needed.
Line 188 - 189		**Comment**: A definition of "all staff members" would be very helpful as it is not really clear if "all employees of the MAH" or "all employees working in the department for pharmacovigilance" are meant?
Line 215 - 220		**Comment**: Competent Authority is not mentioned in the list of sources the MAH shall follow-up information. But for MAH the Competent Authority is a source like the others and in addition reports received from CAs are very often very limited in information. **Proposed change (if any):** Include Competent Authority into the list. (The CA shall follow-up with their source and inform the MAH.)
Line 336 - 344		**Comment**: Why are the job descriptions and the organization chart not explicitly mentioned? **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')*
		We would recommend to add a sentence corresponding to line 326 (job descriptions defining the duties of the managerial and supervisory staff [IM Art 13(1)]) and line 327/328 (organisation chart defining the hierarchical relationships of managerial and supervisory staff [IM 328 Art 13(1)]) to the section I.B.11.2.
Line 434 - 443		**Comment**: It is appreciated that Marketing Authorisation Holders may establish more than one pharmacovigilance system in specific circumstances. **Comment**: There is an intermixture of clearly distinct terms: the "pharmacovigilance system" compromises several, if not all products of a MAH, whereas the risk management systems are clearly related to specific active substances. The sentence including line 439: "A description of PVS shall.....after the marketing authorisation has been granted" reflects only the rare situation of a MAH developing his first product. **Proposed change (if any):** A description of the pharmacovigilance system shall....by the marketing authorisation holder for all marketed products. Development and maintenance of risk management systems is a content of the PVS and starts with the application of product authorisation at the latest.
Line 450 - 454		**Comment**: The QPPV is part of the PVS which usually covers a number of products and not per product (see above). Changes of the QPPV should therefore not require variation of product authorisation, but updates in the

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		pharmacovigilance system master file and in EV registration.
Line 466 - 467		**Comment**: The word “influence” is too weak in that context. **Proposed change (if any):** The word “influence” should be replaced by “direct” or “control” (and the phrase “the performance of” should be deleted).
Line 533 - 534		**Comment:** It is agreed that a back-up procedure should be in place in case of the absence of the QPPV. This back-up might include a variety of processes and depends on the size and the structure of a company. Therefore, it is not acceptable that this should be accessible through the QPPV’s contact details.
Line 570 - 573		**Comment**: In our opinion the validation of a database is a task of the IT department / IT expert and goes beyond the expertise of a pharmacovigilance expert. Thus it is disproportionate to expect that a QPPV is permanently informed about any and all validation issues. Access to e.g. validation records should be sufficient for the QPPV. **Proposed change (if any):** We recommend that the above mentioned sentence should be changed to: “*The adverse reaction database, records regarding the validation status of the database, failures that occurred during validation and 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')*
		corrective actions that have been taken to address the failures should be made available to the QPPV".
Line 592 - 596		**Comment**: The MAH shall check the European medicines web-portal for any relevant updates, including consultations and notifications of procedures. I can only imagine that this could concern another substance from the same class. But even than, if the Agency or a Committee identifies a class effect the MAH of concerned products would be informed directly, probably even prior to publication on the web-portal.
Line 798 - 802		**Comment**: Is is not really clear which terminology is used by whom (MAHs? Authorities? Agency?) and therefore specification is needed.

<Date of submission>

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
Bristol Myers Squibb

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Section I.B.11.3 Critical pharmacovigilance processes: is this section meant to ensure companies have sustainable processes for performing the extensive list of critical PV functions in the situation of prolonged down-time, ie, how does the company handle disaster recovery, longer term in addition to a system failure, shorter term? (long term: benefit-risk evaluation, risk management; short term: processing expedited ICSRs, submit a PSUR that is due, etc.)

2. **Specific comments on text**

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
Celgene Europe Ltd.

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 133 - 134		Comment: Although all persons within an organization should be aware of how to forward adverse events to their PV department, not everyone is otherwise involved in the support of the PV system. Proposed change (if any): "All persons within the organization should be trained on identifying adverse events and their responsibilities for reporting AEs within an organization."
Line 142		Comment: Please provide clarity regarding how an organization would measure "good cooperation" within the context of a quality system. Proposed change (if any):
Line 255		Comment: Reference to all documents is too broad and would prove to be too burdensome in volume alone. Proposed change (if any): "maintained for all essential documents"
Line 463-466		Comment: The need for a National QPPV and their associated responsibilities in relation to those of the EU QPPV should be clarified. Additional language should be added to the module outlining the need for Member States to ensure that the role and responsibilities of the National QPPV as set out in National legislation do not conflict with those of the EU QPPV. Proposed change (if any): Member States that require implementation of National QPPVs should be outlined in chart format and referenced as an appendix. The following text should also be added, "If a Member State imposes requirements for a National Pharmacovigilance contact person (or National QPPV), the Member State

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		shall ensure that the roles and responsibilities of that person as set out in the respective National legislation do not conflict with those of the EU QPPV."
549		Comment: Review and sign-off implies that a "wet signature" is required. The word "approval" would allow for alternative methods to document approval (i.e., e-signatures) Proposed change (if any): "being involved in the review and approval of protocols…."
572-574		Comment: The QPPV's awareness of all system validation failures will unnecessary burden to the QPPV; however, and awareness of the validation status and any corrective actions is appropriate. Proposed change (if any): Delete "including any failures that occurred during validation"
585 - 586		Comment: Reference to the use of terminology should be clarified. Proposed change (if any): Data entry staff should be trained on the use of the database and MedDRA coding with measures in place to verify proficiency.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
Charnley Nickols Associates Ltd

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall a useful summary. However, further detailed review of consistency with the other proposed PV Modules, clarity of cross-references and the precise use of English in this Module is recommended once any modifications of each of the other Modules has been undertaken.

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')*
62		Comment: Article 1 of Directive 2001/83/EC does not provide a definition of a pharmacovigilance system Proposed change (if any): As Annex I – Definitions provides a definition of a PV system (Annex 1 lines 289-296) perhaps this would be a more appropriate reference.
95		Comment: the wording " quality is a concept that can be understood as a degree subject to measurement" is unclear Proposed change (if any):"quality is a matter of degree and is capable of being measured" or "quality can be seen as a parameter or resultant of a series of parameters which can be measured objectively"
98-100		Comment: Philosophically these statements are acceptable but they are not in line with the usual wording of the definitions of quality control and quality assurance – see for example the ICH E6 Guidelines (slightly modified below). Proposed change (if any): **Quality Control (QC):** The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the activities have been fulfilled. **Quality Assurance (QA):** All those planned and systematic actions that are established to ensure that the activities performed and the data are generated, documented (recorded), and reported in compliance with the applicable regulatory requirement(s).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
102-103		Comment: It is not clear that the other modules state precisely, systematically and in a clearly identified way the quality objectives and quality requirements for each of the structures and processes of the PV systems they address.
112		Comment: Quality control is not just the carrying out of tasks and responsibilities but also the 100% checking of their correct performance and outcome
127		Comment: "with the aim to fulfil" Proposed change (if any): "with the aim of fulfilling"
231-235 and 239		Comment: There is no verb in these bullet points
304-305 and 311-312		Comment: 311-312 appears repetitious of 304-305 in its current wording Proposed change (if any): Suggest revisiting lines 297 to 321 to enhance the distinction and clarity of the points being made
346-375		Comment: It is not clear whether this section represents the "required minimum set of written procedures" mentioned in Module II line 355., or does this refer to lines 347 to375 of this module. Proposed change (if any): This module should state quite clearly which section provides the required minimum set of written procedures as discussed in Module II.
340		Comment: It is not clear what is meant here by the term "keep accessible". If it means document and make the documentation accessible then lines 344 and 345 appear to cover this and more. To whom are the organisational structures etc. to be kept accessible?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		What form of access is anticipated?
374		Comment: "or between marketing authorisation…" Proposed change (if any): "and between marketing authorisation…"
388-389		Comment: see comment on lines 102-103
398-399		Comment: states that the PV system is covered by the quality system but lines 104-105 state that the quality system is part of the PV system. Proposed change (if any): If it is agreed that the quality system is part of the PV system and not vice versa then "Audits of the quality system should include audit of the pharmacovigilance system of which it is part".
401-404		Comment: This appears to limit production of the audit report to audits of the pharmacovigilance system of a marketing authorisation holder? What about audits of the PV systems of its delegated subcontractors, license partners – presumably they are to be considered to be part of the MAH PV system? Proposed change (if any): Perhaps this should be stated as part of an additional definition in Annex I of Marketing Authorisation Holder
422		Comment: Developing preparedness plans for public health emergencies "as the need arises" is most probably too late and also it is illogical to describe these as preparedness plans if there is no advanced planning actually involved. I.C.4 merely repeats this illogicality. Proposed change (if any): Plans for public health emergencies should be prepared in advance in the same way that MAHs are expected to have business continuity and disaster recovery plans available in advance. The broader structures can be modified as the emergencies occur or become more imminent but the entire plan should not be developed under emergency or near emergency conditions as it required careful consideration and consultation.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
Chugai Pharmaceutical Company

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

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
I.B.4. :Overall quality objectives for pharmacovigilance: ▪ complying with the legal requirements for pharmacovigilance tasks and responsibilities; • preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; • promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public; and		Among four objectives, latter three objectives seem to be those of PV system. Why does the title contain 'quality', i.e., overall quality objective? Does this mean that 'quality' refers to the quality of PV system, e.g., for signal detection data mining should be used instead of actual number of cases (one death case, three unexpected serious cases, etc.)?
I.B.5. :Principles for good pharmacovigilance practices:All persons involved with the organisation should engage in continuous quality improvement following the quality cycle in		This sentence should read as follows: All persons involved within the organisation should engage in continuous quality improvement following the quality cycle in I.B.3..

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
I.B.3..		
I.B.6. :Responsibilities for the quality system within an organisation:ensuring that changes to the pharmacovigilance system and its quality system are adequately controlled and clearly documented;		What does 'adequately controlled' mean? Does this mean that it is controlled following requirements by health authorities?
I.B.7. :Training of personnel for pharmacovigilance:Adequate training should also be considered by the organisation for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, sales and marketing, regulatory affairs, legal affairs and audits.		Do such activities mean the AE awareness training to any employee mentioned above?
I.B.10. :Record management:		I.B.10 is not referred by any sentence. It would be worth referring to I.B.10 in I.B.6.
I.B.10. :Record management:As		What is the definition and scope of 'all documents used for PV 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')*
part of the quality system, a record management system shall be maintained for all documents used for pharmacovigilance activities, ensuring their retrievability as well as traceability of how safety concerns have been investigated, the timelines for these investigations and how and when decisions have been taken [IM Art 15(1), Art 20(1)].		
I.B.10. :Record management:effective internal and external communication; and		Does this mean the minutes and the communication by e-mail?
I.B.11. :Documentation of the quality system:300 instructions for the compliance management processes (see I.B.9.) [IM Art 14(1), Art 19(1)];		What is the definition of "instruction" ?
I.B.11. :Documentation of the quality system:It is recommended that the documentation of the quality system also includes: • the methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfil the quality		What kind of activity meets the monitoring of the efficient operation of quality system? Should this be done by 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')*
objectives;		
I.B.12.: Monitoring of the performance and effectiveness of the pharmacovigilance system and its quality system:evaluating the effectiveness of actions taken with medicinal products for the purpose of minimising risks and supporting their safe and effective use in patients.		Is the effectiveness of risk MAP appropriate scope of the quality system? This seems that auditor should judge whether the risk MAP is effective or not.

Please add more rows if needed.

17.04.2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
CIS bio international/IBA

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line121		Comment: does “occupational exposure” include manufacturing exposure? (i.e manufacturing, or QC employees of a company). Proposed change (if any):
Lines 197-198		Comment: This is rather imprecise. Some National Authorities (i.e. MHRA) request a PV training for each company employee (incl. manufacturing staff). Proposed change (if any):
Lines399-400		Comment: Is it allowed that the EUQPPV or his deputy audit the local PV organization of a distributor? Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall, this draft module (GVP Module I - Pharmacovigilance systems and their quality systems) is very comprehensive and provides detailed and helpful guidance on the establishment and maintenance of quality assured pharmacovigilance systems. We applaud the Agency for efforts to provide comprehensive guidance. Further, we appreciate the opportunity to review this document and provide the following comments with the goal of improving, and thereby strengthening, the final guidance. **(a) Definitions:** Definitions are presented in both this module and in GVP Annex I (definitions). This organisational duplication increases the risk for definition mismatch, i.e., inconsistencies, and for confusion regarding the location of important definitions. Nevertheless, it is useful to have relevant definitions reproduced in the Module. All GVP definitions should be consolidated in GVP Annex I, wording should be checked for accuracy against applicable reference documents, and fidelity between definitions in the Module and the Annex must be assured. A statement should be added to the introduction of each GVP module, as relevant, indicating that the definitive source of GVP definitions is GVP Annex I. **(b) Scope of document retention** Expectations regarding documents to be considered in scope for the retention requirements are not specified. A description of the relevant documents should be added. See specific comments to line 590 to 592. **(c) Scope of training documentation** The need to document testing/examining of employees after training in standard operation procedures is overly broad. Only key pharmacovigilance processes, such as data entry and coding, should be in scope for this module. Otherwise, normal documentation of training in standard operations procedures should be sufficient.

Stakeholder number *(To be completed by the Agency)*	General comment
	(d) An extra quality manual or just the PV Master File Section I.B.II (Documentation of the Quality System) refers to all elements, requirements and provisions being documented in a systematic and orderly manner in the form of written policies and procedures, such a quality plans quality manuals and quality records. EFPIA appreciates that this is an ISO standard but ISO requirements do not assume the existence of another extensive document such as the PV Master File. It is therefore redundant to create and maintain a separate quality manual when the PV Master File is much more extensive and should fulfil the role of a quality manual. **(e) Abbreviations** The Modules appear to lack a system of introducing abbreviations of key terms and adhering to the system. E.g. lines 61, 685 and 700 abbreviation of GVP; lines 449, 515 and 528 abbreviation of QPPV and lines 718, 731, 739, 763 and 771 abbreviation of CHMP

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 change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
104-108		**Comment:** To avoid redundancy, the general provisions of the PV system and organization as described in the PSMF should not have to be described separately in SOPs as well. The current text may be seen as if the following will have to be described in SOPs, even if also described in the PSMF. Organisational structure Responsibilities, Procedures, processes Resources of the pharmacovigilance system including appropriate resource management, compliance management and record management… EFPIA agree that procedures and processes will need to be described in SOPs but , in order to avoid unnecessary bureaucracy and duplication consider that for the remaining points, the Pharmacovigilance System Master File provided the appropriate procedural part of the quality system **Proposed change:** Replace first sentence with: "***The PV system master file should be an integral procedural part of the quality system***". …. Add after line 108: "***In order to minimise unnecessary duplication and redundancy, the PV system master file should***

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		be an integral procedural part of the quality system and only processes and procedures will require separate SOP documentation."
111		**Comment**: The documentation expectations for quality planning are not clearly articulated in the text, "*Establishing structures and planning integrated and consistent processes (quality planning)*." **Proposed change:** Replace first sentence with: "*Establishing structures and planning integrated and consistent processes (quality planning),* ***as evidenced in SOPs, quality management plans, and procedural documentation***."
133 - 134		**Comment**: The sentence: "*All persons within the organisation should be involved in and support the Pharmacovigilance system on the basis of task ownership and responsibility*", is confusing and could be misleading. While every employee has a responsibility to forward suspected ADVERSE REACTIONs to a pharmacovigilance unit, all employees do not have tasks directly related to day-to-day operational activities in the pharmacovigilance function. **Proposed change:** Revise text to read (two bullets): "~~*All persons within the organisation should be involved in and support the pharmacovigilance 133 system on the basis of task ownership and responsibility*~~.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		"All persons should be trained in forwarding suspected ADVERSE REACTIONs that are being reported to them as company representatives. • ***"All persons within the pharmacovigilance organisation should support the Pharmacovigilance system; the degree of involvement will vary by function, but should be on the basis of roles and responsibilities."***
139-141		**Comment**: The module states that all available evidence should be sought. However, it does not provide guidance on what should be done if the known available evidence cannot be obtained, e.g., if data is known to be available from a trial not sponsored by the MAH and the sponsor is not willing to provide the MAH with the data. Furthermore, we would like to stress the likely impact of vaccine issues on public health. **Proposed change:** Revise to read *"All available evidence on the benefit-risk balance on Public health (e.g. vaccines) of medicinal products should be sought and all relevant aspects, which could impact on the* ***benefit-risk*** *balance and the use of a product, should be considered for decision-making.* ***Where evidence is known to exist, but is not available to the marketing authorization holder, e.g. because it is owned by a third party who is not willing or able to share it with the marketing authorization holder, the marketing authorization holder should provide a brief explanation as to why the data are not available."***
142-144		**Comment:** Although good cooperation with all stakeholders is highly advisable, the advantage of stating this in a regulatory guideline on quality systems seems questionable, as not measurable.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Furthermore, it is not clear what is meant by "learned societies". **Proposed change:** Remove the paragraph, i.e., "~~*Good cooperation should be fostered between marketing authorisation holders, competent authorities, public health organisations, patients, healthcare professionals, learned societies and other relevant bodies in accordance with the applicable legal provisions*~~." .
159		**Comment:** The perceived scope is overly broad. Training should focus on those roles directly linked to the pharmacovigilance system. **Proposed change**: Revise to read: "*Ensuring that adequate resources are available and that* ***appropriate pharmacovigilance*** *training is provided* ***to all employees, depending on the various employees' roles and responsibilities***."
161		**Comment:** "*regular*" is a very loose term when referenced in the following: "*reviewing the PV system including its quality system at regular intervals to verify its effectiveness ...*" **Proposed change:** "*reviewing the PV system including its quality system at* ***"regular risk based"*** *intervals to verify its effectiveness*" (consistent with comment provided for Lines 636 - 637)

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
164 - 166		**Comment:** Between the step "*Ensuring that mechanisms exist*" and the step "*investigating any concern arising*", a step dealing with identifying a concern should be inserted. **Proposed change:** Add a new bullet after line 165: "• ***Identifying concerns regarding non-adherence;****"*
169		**Comment:** Lack of a cross-reference with the specific guideline on audits (Module IV). **Proposed change:** Add the text in italic letters to read: "*Ensuring that edits are performed* ***(see I.B.12. and Module IV)"***
172		**Comment:** "*Motivating all staff members, based on shared values…*" . EFPIA agrees that this is highly desirable, however this level of detail is inappropriate in this type of guidance. Definitions of motivation and how to motivate staff is very subjective and the guidance should be much more objective and focus on activities that will ensure staff members comply with internal processes and legislation to ensure patient safety. **Proposed change:** Remove lines 172 -173: "~~*motivating all staff members, based on shared values, trust and freedom to speak*~~

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		~~*and act with 172 responsibility and through recognition of staff members' contributions within the organization;*~~
191-193		**Comment**: With the current text, we are concerned that inspectors may expect mini-examinations or formal accreditation in every single standard operating procedure. Currently, many companies have exams documented with training certificates in key processes such as data entry, signal detection and MedDRA coding. It is important to highlight that many standard operating procedures cannot be memorised; instead they must be consulted when the tasks, are being performed. **Proposed change:** Limit the scope of competency examination to the selected critical competencies. It is suggested to add the following line. Before line 191: "***There must be a process for ensuring that all employees are trained in all relevant tasks, in addition there should be a process for identification of critical procedures for, which the knowledge and understanding gained after training should be tested***." Line 191 should then be modified as follows: "**For these critical procedures**, there should be a process in place ……."
194		**Comment**: This section should focus on **relevant** training principles and responsibilities for groups not directly involved 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 change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		pharmacovigilance. **Proposed change**: Replace text with: "~~***Adequate***~~ ***Training on principles and responsibilities relating to the pharmacovigilance system*** *should also be considered by the organisation for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned, but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance.*"
255		**Comment:** We are concerned that with the current text the Marketing Authorisation Holder may be expected to retain even draft documents and internal discussions. That is not possible for the following reasons: 1. The practical task of sorting and saving all e-mails will be very burdensome 2. The server space needed will be enormous 3. Comments to draft reports may not exist electronically, as handwritten notes in a print out of the draft document may be used. 4. Not every document used in daily Pharmacovigilance activities is relevant for long term archiving. **Proposed change:** Revise to read as follows: "As part of the quality system, a record management system ~~shall~~ *should be maintained for all* ~~documents used for pharmacovigilance activities~~,***individual case safety report source documents and all final documents related to safety surveillance*** *…..*"
279-280		**Comment:**

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		"*There should be appropriate structures and procedures in place to ensure that Pharmacovigilance data and records are protected from destruction*" should be given greater specificity. **Proposed change:** Revise the text on line 279-280 to read: "*There should be appropriate structures and procedures in place to ensure that pharmacovigilance data and records are protected from destruction* ***during the applicable record retention period*** *(I.C.1.4.)."*
283 – 291		**Comment**: As noted in the general comments, ISO requirements do not assume the existence of another extensive document such as the PV Master File. It is therefore redundant to create and maintain a separate quality manual when the PV Master File is much more extensive and should fulfil this role. **Proposed change:** After Line 291: add an additional sentence: "***For the purposes of the quality system the Pharmacovigilance System Master File and the linked SOPs/procedures of the organisation will fulfil the requirement for a quality manual***."
290-300		**Comment**: The focus should be on training of those with roles directly linked to the pharmacovigilance system described in the GVP modules.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change:: Revise to read (line 298-299): "*documents on organizational structures and assignments of tasks to personnel* ***who support or are directly linked to the organisation's pharmacovigilance system*** (see I.B.11.1. and 298 I.B.11.2.);" Revise to read (line 300): "*training plans and records* ***for personnel who directly support or are directly linked to the organisation's pharmacovigilance system*** *[IM Art 13(1)] (see I.B.7.)[IM Art 13(2), Art 18(2)];"*
292 – 295		**Comment:** In section I.B.11, the organisation is required to define in advance: "*quality objectives specific to their organisations in accordance with the overall quality objectives provided under I.B.4. and the structure and process-specific quality objectives in accordance with each Module of GVP*;" The requirement for creation and maintenance of a quality plan with process-specific quality objectives for each module of GVP seems to be redundant with the more extensive PSMF. The objectives are defined in the modules and each module will have procedures describing the requirements to meet those objectives. EFPIA also note that lines 388-389 state: "*The quality requirements for each pharmacovigilance process are provided in each Module of GVP as appropriate*". The point has already been made about specifying detailed requirements in a separate quality manual. Equally, a separate quality plan with structure and process specific quality objectives in accordance with each module should also not be necessary with the very detailed requirements of the Master File and the SOPs supporting each Module.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Replace text with: "*quality objectives specific to their organisations in accordance with the overall quality objectives under I.B.4* ~~***and the structure and process specific quality objectives in accordance with each module of GVP***~~ **....**
296-297		**Comment:** We fear that the text "*The quality system shall be documented by: Documents on organisational structures and assignments of task to personnel*" may be interpreted as if Individual named employees must be listed. **Proposed change::** *"The quality system shall be documented by:* • *Documents on organisational structures and assignments of task to departments or virtual functions* ***concerned in PV tasks."***
306		**Comment:** The text refers to "*quality audits*". In the remainder of the module, the term "audit" is please. Please clarify if the nature of the quality audits, if not synonymous with audits. Furthermore, the meaning of "*follow-audits*" is unclear. **Proposed change:** Replace text with: "***Reports of audits and follow-up checks on the effectiveness of corrective actions, including their dates and results."***

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
313-314		**Comment:** "*Records created as a result of Pharmacovigilance processes which demonstrate that* ***all*** *steps required by the defined process have been taken …*" The amount of documentation needed will be unreasonable high, if all steps should be documented **every time**. The focus should be on the job and not on the control. It should be documented that all steps have been conducted e.g. by signature, but not all steps should be signed off every time. In addition it is not every time a process is run e.g. safety surveillance that all steps are taken, it depends on the data, situation etc. **Proposed change:** Suggest removing the last words, the sentence will read as follows: "*Records created* ~~as a result of pharmacovigilance processes~~ *which demonstrate that* ~~all steps required by the defined procedures have been taken~~ ***the defined pharmacovigilance process has been conducted***;"
326		**Comment**: Use of resource management without any qualification is unclear as it could cover a wide variety of areas e.g. financial management. EFPIA note that in Article 11 of the draft Commission Implementing Regulation published on 2 April, the scope is clear so we recommend that some examples are provided in the GVP module for clarity. **Proposed change**: Revise text to read: "*their resource management* ***e.g. job descriptions of supervisory and managerial staff, including the QPPV and organisational charts, training and appropriate instructions on processes*** *[IM Article 13(4)]"*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
333-334		**Comment**: "*It is recommended that the documentation of the quality system additionally includes the organisational structures and assignments of tasks, responsibilities and authorities to all personnel*". The text gives raise to four issues: It is not clear whether organisational documentation of the pharmacovigilance system needs to be maintained specifically as a part of the Quality System or just maintained in general as part of the PSMF. The meaning of "recommended as opposed to shall and should is not clear". "..to all personnel.", may be seen as referring to endless list of named persons. The meaning of the word "authority" is not clear. **Proposed change**: Replace text with: "~~*It is recommended that the documentation of the quality system additionally includes the organisational structures and assignments of tasks, responsibilities and authorities to all personnel.*~~ ***The quality system should maintain documentation of organizational structure, assignment of tasks and responsibilities supporting its pharmacovigilance system***."
396		**Comment:** "*risk-based audits of the quality system itself shall be performed at regular intervals*". If a risk based approach is to be used for auditing then also stipulating a regular interval contradicts this. Taking a risk-based approach means you would not necessarily follow a regular interval, as you would focus attention where the biggest risk occurs and so each year the area of focus may 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 change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Revise to read: "*Risk-based audits of the quality system shall be performed ~~at regular intervals~~ to assure that it complies with the established quality requirements and to determine its effectiveness* ".
467-469		**Comment:** The text currently states: "*The MAH should therefore ensure that the QPPV has access to the PSMF as well as authority over it and is notified of any changes to it".* As per the PSMF module, the QPPV does not need to be notified of <u>all</u> changes to the PSMF. **Proposed change:** Change text to read: "*The MAH should therefore ensure that the QPPV has access to the PSMF as well as authority over it and is notified of any changes to it* ***in accordance with Module II (lines 158-173)."***
493		**Comment:** For a big company with hundreds of affiliates and partners being audited and inspected regularly, the documentation which the QPPV have to review should be limited to a minimum. **Proposed change:** Revise to read: "~~*A copy of the corrective and preventive action plan*~~ ***A list of critical and major findings, findings with corrective and preventive action plans***".

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
527		**Comment:** The expression '*natural person*' is not clear. **Proposed change:** If the intention of the sentence is that the EU-QPPV should be an EU citizen, please amend accordingly. *The qualified person responsible for pharmacovigilance in the EU (QPPV)* ~~*is a natural person.*~~ ***should be an EU citizen.***
542		**Comment:** "*specific additional responsibilities of the QPPV should include*:" Will it be acceptable to delegate some of these activities as is currently the practice under volume 9A and as stated in Module 2 on Master File (PSMF)? The QPPV tasks, which are delegated, should be included in the pharmacovigilance system master file, see excerpt from draft Module II below. This implies that QPPV tasks can be delegated. Text from Module 2 - II.B.4.1. PSMF section on qualified person responsible for pharmacovigilance (QPPV): *"A list of tasks that have been delegated by the qualified person for pharmacovigilance shall also be included in the Annexes (see II.B.4.8.), and this should include a description of the activities that are delegated and to whom."*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Replace text with: "*specific additional responsibilities of the QPPV, **which may be delegated**, should include:*"
548-549		**Comment:** "*being involved in the review and sign-off of protocols of post-authorisation safety studies*". This indicates that the EU QPPV (or delegated employee) should sign off the study protocol. Other mechanisms than a wet-ink signature should be allowed for either electronic signature or e.g. approval via e-mail. **Proposed change:** Replace text with: "*being involved in the review and ~~sign-off~~ **approval** of protocols of post-authorisation safety studies*"
561-562		**Comment:** The input of the QPPV should be focused on safety variations due to emerging safety concerns. We suggest specifying this in the document. **Proposed change:** Replace text with: "*Providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. **safety** variations, urgent safety restrictions, and communication to patients and health professionals)*."
572-574		**Comment:**

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; **Proposed change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		We agree that the QPPV should be aware of the validation status of the database, however, we are concerned that it will add unnecessary burden to the QPPV to be informed of any failure during the validation and the corrective actions that have been take. **Proposed change:** Replace text with: "***the QPPV should be aware of the validation status of the database, including any significant failure that occurred during validation and any corrective actions that have been taken***"
585		**Comment:** We have concerns regarding the documentation needed to demonstrate that data entry staff has been tested in the understanding of the use of various terminologies. **Proposed change:** Replace with: "***Data entry staff must be instructed and examined in the use of the database. Furthermore, staff performing MedDRA coding must be trained in their proficiency verified***."
590-592		**Comment:** "*…pharmacovigilance data and documents relating to authorised medicinal prod*ucts…." Our concern is <u>not</u> about the retention time of 10 years, our concern is the <u>scope</u> of pharmacovigilance data and documents related to the medicinal product. **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 change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Revise text to read: **"**the retention of ~~pharmacovigilance data and documents~~ ***.all essential documents related to critical PV activities (see I.B.11.3)*** ~~relating to authorised medicinal products~~ as long as the marketing authorisation ***…."*,** ***or with*** **"**the retention of ~~pharmacovigilance data and documents~~ ***all individual case safety report source documents, all final documents related to safety surveillance, labelling updates, and product recalls*** ~~relating to authorised medicinal products~~ as long as the marketing authorisation***…."***
593		**Comment:** We are concerned that the public may become aware about updated information on the web-portal before the MAH. Please, ensure that the MAH also get or can sign up to get direct notification. **Proposed change:** Replace text with: "*that the product information is kept up-to-date with current scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal. To this end, the marketing authorisation holder shall continuously check the European medicines web portal for any relevant updates, including consultations and notifications of procedures [IM Art 596 14(1)(e)].* ***It should be possible for the MAH also to receive direct notification of the updated information.****"*
593-597		**Comment**: Checks should be done on a regular basis. Practical aspects of incorporating 'c*ontinuously*' into a process or related procedure are daunting. **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 change:**s *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Revise to read (lines 594-597): "*To this end, the marketing authorisation holder shall* ***~~continuously~~*** ***regularly*** *check the European medicines web-portal for any relevant updates, including consultations and notifications of procedures [IM Art 596 14(1)(e)].*"
636 – 637		**Comment**: "*Regular audits*" is an imprecise term. Suggest the use of "risk based" audits. **Proposed change:** *"In this respect,* ***"regular risk-based"*** *audits of the other organisation by the marketing authorisation holder or introduction of other methods of control and assessment are recommended*." (consistent with comment provided for Line 160)

Please add more rows if needed.

17 April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
EGA - European Generic Medicines Association

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

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

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1. General comments

Stakeholder number (To be completed by the Agency)	General comment
	In general the guidance as written in this GVP module is very detailed. It should be kept in mind that MAH have in general databases for example regulatory affairs, complaints which are validated and have an audit trail. This does not mean that for changes in such a system “controlled documents” are available on every change. This is the same for the audit trail / controlled changes for the PSMF, which would mean that several times a day a controlled document should be updated when there is a change in one of the appendices. The quality system should guarantee quality of reports and data and should guarantee quality and uniformity of the pharmacovigilance processes. A quality system in pharmacovigilance activities should not turn out to be a bureaucratic monster where several administrative assistants are only printing and tracking documents. The way it is described now the primary goals of the new legislation “simplification” and “reducing bureaucracy” are definitely not met.
	A heavy task is been put on the shoulders of the QPPV in these guidelines. The QPPV should reflect to safety issues and is not responsible for training people within the entire company. This would be the responsibility of the MAH, the company or its training department.

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 62-66		Comment: 'The definition of a pharmacovigilance system is provided in Article 1 of Directive 2001/83/EC as a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance. The Agency likewise maintains a pharmacovigilance system to fulfil its pharmacovigilance activities.' Proposed change (if any): Amends for readability. 'The definition of a pharmacovigilance system is provided in Article 1 of Directive 2001/83/EC as a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX. The pharmacovigilance system is designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance. The Agency likewise maintains a pharmacovigilance system to fulfil its pharmacovigilance activities.'
Lines 122-124		It is not the quality objective of pharmacovigilance to promote the "effective" use of medicinal products. Proposal: Promoting the safe ~~and effective~~ use of medicinal products, in particular through providing …..
Line 131 and 132		Comment: "Higher management should provide leadership in the implementation of the quality system and motivation for all staff members in relation to the quality objectives" Please rephrase to match the Volume 9A wording. Proposed change (if any): Quote Volume 9A: "The Marketing Authorisation Holder should adequately support the QPPV and ensure that there are appropriate processes, resources, communication mechanisms and access to all sources of relevant

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')
		information in place for the fulfilment of the QPPV's responsibilities and tasks."
Lines 142-144		There is no legal basis for the whole sentence with special regard to cooperation with patients or healthcare professionals. This is nothing more than a good wish and therefore not appropriate for guidance on a legal text. Proposal – deleted the last bullet. ~~Good cooperation should be fostered between marketing authorisation holders, competent authorities, public health organisations.....~~
Line 156		Comment: Define what is meant by "quality systems are adequately controlled". Proposed change (if any): It will be more informative if there is description of what is required to be "adequate" (e.g. specific monitoring with frequency etc.).
Lines 180-181		Comment: 'All personnel involved in the performance of pharmacovigilance activities shall be provided with appropriate instructions on critical processes, including business continuity [IM Art 13(3), Art 18(3)].' There are two comments on this section. Firstly in general all employees of a MAH play a role in the performance of pharmacovigilance processes and they should be appropriately trained. For the so called first receivers (i.e. sales reps, med info RA, legal etc) there is definitely no need to be aware of and trained in business continuity. There initial contact for internally reporting adverse events should be available. Secondly for the easiness of reading, the critical processes can be referred to the appropriate section. Proposed change: Line 180 and 181 should be replaced by: All personnel possibly involved in initially receiving adverse events should be appropriately trained in the processes they have to conduct. All personnel involved in the further

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')
		collating, assessing and reporting and further pharmacovigilance processes should be appropriately trained and receive instructions on critical processes (see I.B.11.3), including business continuity [IM Art 13(3), Art 18(3)].
Lines 186 - 189		It is stated that the training for “all” personnel should support continuous improvement of skills, application of scientific progress and professional development. These training goals are not relevant to all PhV personnel and it makes no sense to require from an administrative worker in PhV that (s)he has a training program improving the application of scientific progress. Proposed change: The training should, *where relevant*, support continuous improvement of relevant skills, the application of scientific progress and professional development. *The training should further* ~~and~~ ensure all staff members have *or gain* the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities.
Lines 191-193		Comment: ‘There should be a process in place within the organisation to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, and in line with agreed professional development plans.’ Proposed change (if any): Amends for readability. ‘There should be a process in place within the organisation to check that training results at the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities are in line with agreed professional development plans.’
Lines 203-210		Comment: This whole section is out of line with the intentions of the document. A perfect quality system and perfect

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')
		pharmacovigilance can be organised independent from facilities and equipment. Location, design, construction, maintenance is completely irrelevant and should not be detailed in EMA guidance. The whole section should be deleted or rewritten in a way that location and equipment should be taken into account in the business continuity program.
Lines 216-220		Comment: '…shall follow-up such information, as appropriate, independent of its source, including information spontaneously reported by patients or healthcare professionals, published in medical literature, or arising in the context of a post-authorisation study.' Information from literature should not be followed up by the MA holder. Case reports in literature are in general well documented. Follow up requests for literature is an unnecessary burden to the author and does not add anything to the safety for the patients. The word "as appropriate" in this sentence is not enough. This will be interpreted as always in inspections. In serious emerging new safety issues it will be part of standard pharmacovigilance to get as much information as needed from all sources – that will facilitate that in needed cases the MAH will go to an author. Therefore the part on literature should be deleted from this paragraph. Propose: "…. shall follow-up such information, as appropriate, independent of its source, including information spontaneously reported by patients or healthcare professionals, ~~published in medical literature,~~ or arising in the context of a post-authorisation study
Lines 243-244		There should also be a requirement for a quality system to ensure that <u>follow up</u> is conducted by the competent authorities of any information as appropriate as reported to them from any source, including spontaneous reports from HCP and patients. The omission of this is not in line with the intentions of the legislation. Furthermore if MS receive cases for products for which the MA holder is required to do additional follow up,

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')
		questionnaires or tests it should be the responsibility of the MS to forthwith notify the MA holders so appropriate actions can be taken. Proposal – change bullet one: Ensure the evaluation and submission of the quality, including completeness of pharmacovigilance data *received from spontaneous sources whereby the MS shall follow up such information as appropriate, independent of its source and ensuring the cases*. Add bullet: *The MS receiving spontaneous adverse events from all sources on product event combinations under close surveillance with the need to conduct additional pharmacovigilance activities should forthwith inform the MA holder so the appropriate actions can be taken according to the risk management plan of the product.*
Line 346		Comment: The bullets in this section describe the complete pharmacovigilance process – it does not make sense to define parts as critical when there are no non-critical processes.
Lines 373 - 375		Comment: 'back-up systems for urgent exchange of information within an organisation, amongst organisations sharing pharmacovigilance tasks or between marketing authorisation holders and competent authorities...' There is no need for such a backup system for interaction with authorities and other MAH, and the requirement therefore introduces bureaucracy, complication and needless money and resources. If there is an urgent exchange of safety information needed through the contract and through the pages on the web portal for every MA holder contact details are available to contact the company. A second backup system therefore is not needed. Proposed change (if any): Delete the requirement

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To 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 438 - 442		Comment: A PSMF is developed today usually not only for one MAH but a number of MAHs belonging to the same corporation. Proposed change (if any): It should be clarified that affiliated MAHs belonging to the same corporation can group into one PSMF.
Line 450		Comment: The marketing authorisation holder shall submit the name and contact details of the QPPV to the competent authorities in Member States and the Agency [DIR Art 104(3) last paragraph]. Changes to this information should be submitted in accordance with Regulation (EC) No 1234/2008 on variations to the terms of marketing authorisation and the Communication from the Commission - Guideline on the Details of the Various Categories of Variations to the Terms of Marketing Authorisations for Medicinal Products for Human Use and Veterinary Medicinal Products Proposed change (if any): The submission of the contact details of the QPPV and the location of the PSMF should be narrowed down as this triggers many variations. These details should be completely covered in the EVMPD database only and a reference can be made to this updated information. This should be made available for NCA and other parties that require this information.
Line 457		Comment: 'Information relating to the QPPV shall be included in the pharmacovigilance systems master file (PSMF) [IM Art 4(1)(a)] (see Module II).' Proposed change: These requirements are described in Module II. There is no need to repeat in this module. The sentence can be deleted
Lines 492 - 494		Comment and proposed change to align with lines 489-490 and to assure the QPPV gets all information as

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')
		required: 'The managerial staff should provide the QPPV with a copy of the corrective and preventive action plan following each audit in the EU or relevant to the EU, so that the QPPV can *be* assure*d* that appropriate corrective actions are implemented.'
Line 549		Comment: The QPPV should be involved in the review and sign-off of protocols of post-authorisation safety studies; Clarifications is needed Proposed change (if any): The QPPV should be involved in the review and sign-off of protocols of post-authorisation safety studies conducted in the context of an EU RMP
Lines 557 – 559, 560 - 561		"Ensuring a full and prompt response to any request from the competent authorities in Members States and from the Agency for the provision of additional information necessary for the evaluation of the benefits and risks of a medicinal product' 'providing any other information relevant to the benefit-risk evaluation to the competent authorities in Members States and the Agency;" The above suggests that the QPPV could be seen as the only point of contact for all efficacy information which would normally go through regulatory affairs and other relevant departments. Sentences should be changed to indicate the QPPV is not responsible for RA/medical/clinical. Proposed change (if any): "Ensuring a full and prompt response to any relevant request from the competent authorities in Members States and from the Agency for the provision of additional information necessary for the evaluation of the safety part of the benefits and risks of a medicinal product' 'providing any other relevant safety information relevant to the benefit-risk evaluation to the competent authorities in Members States and the Agency;"

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')
Lines 572 - 574		'…including any failures that occurred during validation and the corrective actions that have been taken to address the failures' This goes far beyond the legal obligations. A QPPV is not a specialist in validation. The QPPV should know that the system is validated. Only validated systems can be used for pharmacovigilance systems. What happens during the development of a system is not the task of the QPPV. Proposed change (if any): delete this part of the sentence ~~including any failures that occurred during validation and the corrective actions that have been taken to address the failures'~~
Lines 587-589		Comment: '…the retention of essential documents describing the pharmacovigilance system as long as the system described in the pharmacovigilance system master file (PSMF) exists and for at least further 5 years after it has ceased to exist [IM Art 15(4)];' Proposed change (if any): the essential documents of the PSMF should be defined precisely. Annexes should be excluded from retention.
Lines 593-597		Comment: '…including the assessments and recommendations made public via the European medicines web-portal. To this end, the marketing authorisation holder shall…' Proposed change (if any): European medicines to European Medicines Agency Website or the Agency Website. European Medicines Agency is already defined as 'the Agency'.
Lines 608-609		Comment: '…the marketing authorisation holders shall define the duties of the QPPV in a job description'.

Line number(s) of the relevant text (e.g. Lines 20-23)	Stakeholder number (To be completed by the Agency)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')
		This is redundant to line 456 Proposed change (if any): Either delete here or line 456.
Lines 630-633		Comment: “When preparing contractual arrangements, the MAH… together with for example, agreed definitions, tools, assignments and timelines.” To avoid endless listings of definitions it is highly recommended to refer to the annex I in the GVP. To avoid misunderstanding the sentence can be clarified Proposed change: When preparing contractual arrangements, the MAH….. together with for example, the reference *used* for agreed definitions, tools, assignments and timelines.
Lines 639-645		Comment: States that the use of two or more commercial designs for a given medicinal product covered by a single marketing authorisation is not prohibited by the Regulation. Such products are called duplicates. Could you explain better the concept of “duplicate”? It will be also useful for us to know some related examples.
Lines 686 - 687		Replace “one Member states” by singular “Member State”
Line 743		Comment: ‘monitoring **selected** medical literature for reports of suspected adverse reactions…’ How will MAHs access this data for literature potentially on their products? It is not clear in this Module and Module VI how suspected adverse reactions will be filtered down to MAHs, so how MAHs should access them (if there is even a need). The process of literature searching needs to be clear with a list of what publication sites will be checked, for

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18-April-2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Comment 1: This Module is an overarching module and refers to the other Modules for the "quality" system aspects of specific PV activities addressed by those Modules. With only half of these modules available, there are considerable gaps in the current understanding of what might be expected in relation to: audit, additional monitoring, continuous pharmacovigilance, referrals etc.
	Recommendation regarding Comment 1: Guidance on the application of new standards (date of application and the regulators' expectations of the performance of activities by Marketing Authorisation Holders) should be issued prior to July 2012 and should represent the interim position of all Member State inspectorates.
	Comment 2: Use of terminology in the Module should be improved: • Definitions for some terms are given, but not in fact employed in the Module e.g. the central definitions of "Quality Assurance" and "Quality Control" (lines 98-9 see also Modules Annex 1). • Some terms are not defined even though they are relevant to the assumption of specific responsibilities e.g. "higher management" (line 130 et seque) and "management/managerial staff" (line 150 et seque). • It would be helpful to provide clarity on the definitions of "Quality Plan", "Quality Manual" and "Quality Record" in section I.B.11 and the relationships between these documents so that it is clear what features are key to each document type and which elements should be addressed in each.
	Recommendation regarding Comment 2: Redundant terms and definitions should be deleted from this and other Modules. Definitions should be in line with definitions in Annex 1. Further guidance should be included with regard to the content and scope of "Quality Plan", "Quality Manual" and "Quality

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

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 98-99 and line 130 et seque and line 150 et seque		Comment: Definitions for some terms are given but not in fact employed. Some terms are not defined even though they are relevant to the assumption of specific responsibilities. Proposed change (if any): Ensure completeness of definitions, deletion of redundant terms and definitions and consistent use of terminology.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	In this draft Guideline on good pharmacovigilance practices (GVP) Module I - Pharmacovigilance Systems and their quality systems “Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC” is cited which is however not yet finalized. Therefore, the comments can only be preliminary.
	It is agreed that a pharmacovigilance system must be quality assured. However, the requirements and provisions have to be proportional to the risk of the products placed on the market by a marketing authorization holder. The administrative burden on the companies must be proportionate to the expected benefit for public health. As an example the requirements in section I.B.11 can be mentioned. *“All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records.”* These requirements may be appropriate for a global company with a complex structure and with innovative products for which the risks are not known. For smaller companies acting mainly on a national level and having products with a low and well known risk such requirements pose significant challenges to implement while offering little benefit.
	Overall a strengthening of the duties of the Marketing Authorization Holder (managerial staff) and the QPPV was noticed and more documentation is needed to be compliant with the Module (e.g. job descriptions for managerial and supervisory staff, definition of key performance indicators).

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 78 - 80		**Comment**: The difference between the verb for the legal requirements „shall" and the verb for the implementation of legal requirements "should" is not really clear and thus clarification is needed.
Lines 133 - 134		**Comment:** Although all persons within an organization should be aware of how to forward adverse events to their PV department, not everyone is otherwise involved in the support of the PV system. **Proposed change (if any):** "All persons within the organization should be trained on identifying adverse events and their responsibilities for reporting AEs within an organization."
Line 142		**Comment:** Please provide clarity regarding how an organization would measure "good cooperation" within the context of a quality system. **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 153 - 155		**Comment**: It is unclear how the “managerial staff” is rather responsible for the quality system than the “QPPV”? Furthermore a definition for “managerial staff” is needed.
Line 188 - 189		**Comment**: A definition of “all staff members” would be very helpful as it is not really clear if “all employees of the MAH” or “all employees working in the department for pharmacovigilance” are meant?
Line 215 - 220		**Comment**: Competent Authority is not mentioned in the list of sources the MAH shall follow-up information. But for MAH the Competent Authority is a source like the others and in addition reports received from CAs are very often very limited in information. **Proposed change (if any):** Include Competent Authority into the list. (The CA shall follow-up with their source and inform the MAH.)
Line 255		**Comment:** Reference to all documents is too broad and would prove to be too burdensome in volume alone.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): "maintained for all essential documents"
Line 336 - 344		**Comment**: Why are the job descriptions and the organization chart not explicitly mentioned? **Proposed change (if any):** We would recommend to add a sentence corresponding to line 326 (job descriptions defining the duties of the managerial and supervisory staff [IM Art 13(1)]) and line 327/328 (organization chart defining the hierarchical relationships of managerial and supervisory staff [IM 328 Art 13(1)]) to the section I.B.11.2.
Line 434 - 443		**Comment**: It is appreciated that Marketing Authorization Holders may establish more than one pharmacovigilance system in specific circumstances. **Comment**: There is a mixture of clearly distinct terms: the "pharmacovigilance system" comprises several, if not all

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		products of a MAH, whereas the risk management systems are clearly related to specific active substances. The sentence including line 439: "A description of PVS shall.....after the marketing authorisation has been granted" reflects only the rare situation of a MAH developing his first product. **Proposed change (if any):** A description of the pharmacovigilance system shall....by the marketing authorisation holder for all marketed products. Development and maintenance of risk management systems is a content of the PVS and starts with the application of product authorisation at the latest.
Line 450 - 454		**Comment**: The QPPV is part of the PVS which usually covers a number of products and not per product (see above). Changes of the QPPV should therefore not require variation of product authorisation, but updates in the pharmacovigilance system master file and in EV registration.
Line 463 - 466		**Comment:** The need for a National QPPV and their associated responsibilities in relation to those of the EU QPPV should be clarified. Additional language should be added to the module outlining the need for Member States to ensure that the role and responsibilities of the National QPPV as set out in National legislation do not conflict with those of the EU QPPV. **Proposed change (if any):** Member States that require implementation of National QPPVs should be outlined in chart format and referenced as an appendix. The following text should also be added, “If a Member State imposes requirements for a National Pharmacovigilance contact person (or National QPPV), the Member State shall ensure that the roles and responsibilities of that person as set out in the respective National legislation do not

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		conflict with those of the EU QPPV."
Line 466 - 467		**Comment**: The word "influence" is too weak in that context. **Proposed change (if any):** The word "influence" should be replaced by "direct" or "control" (and the phrase "the performance of" should be deleted).
Line 533 - 534		**Comment:** It is agreed that a back-up procedure should be in place in case of the absence of the QPPV. This back-up might include a variety of processes and depends on the size and the structure of a company. Therefore, it is not acceptable that this should be accessible through the QPPV's contact details.
Line 549		**Comment:** Review and sign-off implies that a "wet signature" is required. The word "approval" would allow for alternative methods to document approval (i.e., e-signatures) **Proposed change (if any):** "being involved in the review and approval of protocols…."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 570 - 573		**Comment**: The QPPV's awareness of all system validation failures will unnecessary burden to the QPPV; however, and awareness of the validation status and any corrective actions is appropriate. Furthermore, the validation of a database may require the expertise of an IT expert that goes beyond the expertise of a pharmacovigilance expert. Thus it is disproportionate to expect that a QPPV is permanently informed about any and all validation issues. Access to e.g. validation records should be sufficient for the QPPV. **Proposed change (if any):** We recommend that the above mentioned sentence should be changed to: "*The adverse reaction database, records regarding the validation status of the database, failures that occurred during validation and the corrective actions that have been taken to address the failures should be made available to the QPPV" / at least the provision* "including any failures that occurred during validation" should be deleted.
Line 585 - 586		**Comment:** Reference to the use of terminology should be clarified. **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')*
		Data entry staff should be trained on the use of the database and MedDRA coding with measures in place to verify proficiency.
Line 592 - 596		**Comment**: The MAH shall check the European medicines web-portal for any relevant updates, including consultations and notifications of procedures. Is “relevant” to be understood that this could concern only another substance from the same class? Even then, if the Agency or a Committee identifies a class effect the MAH of concerned products would be informed directly, probably even prior to publication on the web-portal.
Line 798 - 802		**Comment**: It is not really clear which terminology is used by whom (MAHs? Authorities? Agency?) and therefore specification is needed.

From: [redacted]
Sent: 18 April 2012 09:38
To: GVP public consultation
Cc:
Subject: EVM Reply to the public consultation of the first batch of modules on good pharmacovigilance practices (GVP)
Importance: High

Subject: Reply to the public consultation of the first batch of modules on good pharmacovigilance practices (GVP)

Dear Madam, dear Sir,

EVM welcomes the opportunity to reply to the public consultation of the first batch of modules on good pharmacovigilance practices (GVP).

EVM is in agreement with the general comments submitted by EFPIA and has submitted the comments on modules I and II together with the EFPIA comments.
Modules V, VI, VII, VIII, IX and Annex I, attached to this email, have been replied separately.

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

Finally, please find below the EVM replies to the modules for consultation.

Kind regards,

[redacted]

[redacted]
European Vaccine Manufacturers (EVM)
[redacted]

www.evm-vaccines.org

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18/04/12

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
Faculty of Pharmaceutical Medicine

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E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Clarify the difference between Quality System and PV System throughout this document

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 5 – section I.B.4		Comment: Change the order of importance – safety should be before legal requirements Proposed change (if any): □ preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; □ complying with the legal requirements for pharmacovigilance tasks and responsibilities;
Page 6 – line 155		Comment: For clarity change managerial staff to management – throughout the document Proposed change (if any): management should be responsible for:
Page 8 – line 222		Comment: Insert “to” before patients Proposed change (if any): all information on the risks of medicinal products as regards to patients’ or public health, including
Page 10 – line 293		Comment: the term “quality objectives” appears 3 times in one sentence Proposed change (if any): rewrite
Page 10 – line 326		Comment: clarify what resource documentation is

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any):
Page 12 – line 391		Comment: For clarity change managerial staff to management – throughout the document Proposed change (if any):
Page 14 – line 463		Comment: Please provide a list of the countries that require a local QP for PV to be appointed Proposed change (if any): further information requested
Page 14 – line 487		Comment: For clarity change managerial staff to management – throughout the document Proposed change (if any):
Page 15 – line 492		Comment: For clarity change managerial staff to management – throughout the document Proposed change (if any):
Page 15 – lines 502 to 504		Comment: for the following sentence - When a marketing authorisation holder intends to expand its product portfolio, for example, by acquisition of another company or by purchasing individual products from another marketing authorisation holder, the QPPV should be notified early in the due diligence process in order – this is not always possible due to confidentialities Proposed change (if any): consider revising the text
Page 15 – line 528		Comment: - what is a natural person Proposed change (if any): clarification

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 17 – line 585		Comment: add “the before this sentence Proposed change (if any): the monitoring of the use of terminology, with data entry staff being instructed in the use of terminology
587 - 589		Comment: This section provides guidance on the timelines for retention of essential documents describing the PV system. Proposed change (if any): It would be helpful if this document provided guidance on what was considered an essential document for this purpose.
589		Comment: This line and various others refer to the Implementing Measures. It is confusing to have two documents to describe the same processes, especially when they appear to contradict each other – see comment below. Proposed change (if any): Incorporate all relevant information from the Implementing Measures into this and other GVP guidelines, as applicable.
587 – 589 590 - 592		Comment: The timelines given in this section for the retention of PV system and product related documents (5 & 10 years respectively) do not agree with the timelines in the draft IM article 15 (10 and 30 years respectively). Proposed change (if any): Please clarify the required timelines.
Page 18 – line 618		Comment: add “to ensure” to this sentence

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): holder to another organisation, the marketing authorisation holder shall retain responsibility to ensure that an
Page 18 – line 625		Comment: add ”the” Proposed change (if any): included in the pharmacovigilance system master file (PSMF) [IM Art 4(1)(f)] and a list of the contractual
Page 22 – line 800		Comment: remove “for” from the end of the sentence Proposed change (if any): and the Agency shall put in place the following additional specific quality system processes:

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
Gilead Sciences International Limited

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
104		Comment: The paragraph pertaining to what the quality system should cover, could include text to state: ”and will be described within the PV Master File”.
112		Comment: carrying out tasks is not “quality control”. ICH GCP define quality control as “The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the activities have been fulfilled” Proposed change (if any): remove “quality control” from the end of the line and add a new bullet describing “quality control” process.
120		Comment: Should read preventing or minimising harm.
133		Comment: Already encompasses all company personnel. 135 appears to be more relevant thereafter to pharmacovigilance personnel in the organisation.
155		Comment: Please clarify the documentation is within the PV Master File.
169		Comment: Please clarify audits of the PV system.
170-173		Comment: Proposed text reads as a HR manual and is not applicable to PV processing. Too much depth.
191-193		Comment: This text suggests the requirement for competency checks on all PV training which can be applied to training provided by the company – but not all external training as there may be no provision for testing.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
282		Comment: The scope and intent of each of the quality plans, quality manuals and quality records requires clarification on expectation and possible content as the current description is unclear.
286-291		Comment: The concept of a quality cycle and CAPA management system is justified. However, we don't see the need for a quality plan as the quality objectives are driven by legislation/requirements and also by internal compliance initiatives i.e. performance metrics, CAPA management, audit. A quality manual would not provide additional value given most MAHs describe the quality system within SOPs.
308		Comment: Please provide further clarity on the retention records for training "plans" (versus training "records") as it is unclear how long the plans should be held for.
326		Comment: Please clarify what is expected with respect to documenting resource management.
350-369		Comment: Please clarify that 349 through 368 are what procedural documents should cover and that BCP is required to show planning for a disaster but not all listed processes will be covered in such continuity planning e.g. system vs. pandemic situations will differ as to what can be reasonably supported.
456		Comment: Responsibilities of a QPPV may only be part of a role and it should be sufficient to define responsibilities in procedural documents and acknowledge in the job description that the person performs the responsibilities of QPPV per internal SOPs.
502		Comment: Pharmacovigilance but not specifically the QPPV should be notified early in due diligence processes.
585		Comment: What is terminology in the context of this section – database conventions or MedDRA? Please

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		clarify.
807		Comment: If action is taken will the MAH also be notified?

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
H. Lundbeck A/S

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1. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
161, 166, 233, 318, 405, 492		Comment: Use of term ”preventative" and "preventive". Module I use term “preventive” however in Module II term “preventative” is used. Proposed change (if any): Please consider harmonising use of term ”preventative" and "preventive" within the Modules
283-284, 296		Comment: It is unclear how detailed the Quality system should be (Quality plans, quality manuals and quality records) Proposed change (if any): Please consider to clarify further
306 and 402		Comment: The text refers to “follow-audits” Please consider rewording. Proposed change (if any): Change text to “follow-up audits”
306		Comment: The text refers to “quality audits”. In the remainder of the module, the term “audit” is please. Please clarify if the nature of the quality audits if not synonymous with audits. Proposed change (if any): Propose to used the term “audit”
317-320		Comment: It is unclear should this include corrective and preventive actions from audits? Unclear how detailed this should be if this is the case. Proposed change (if any) Please clarify the requirement

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
279-280		Comment: PV record retention period is described in paragraph I.C.1.4 (line 589-591 and 597-598). However line 279-280 state “There should be appropriate structures and procedures in place to ensure that Pharmacovigilance data and records are protected from destruction”. Proposed change (if any): Please consider changing the text on line 279-280) to “There should be appropriate structures and procedures in place to ensure that pharmacovigilance data and records are protected from destruction during the applicable record retention period (I.C.1.4.).

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The use of “risk-benefit” or “benefit-risk” should be harmonized to “benefit-risk” throughout the document (e.g. line 65 versus 350 and 478)
	The only point in the document that references the importance of interlinking organisations in the PV system is in lines 194-198. This section relates to training – however, a lot of the other sections are also being important for interlinking organisations to ensure they have appropriate controls in place e.g. IB5, IB6, IB9.2, IB11.2 etc. Proposed change (if any): A catch all statement at should be added at the start of the document indicating that although the focus of the document is on pharmacovigilance systems, any “supporting” functions who contribute to the PV system should also ensure they have appropriate “Quality and Compliance” systems in place to assure the QPPV that their systems and processes are in control/compliance.

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 120-121		Comment: The use of the word “Preventing” is suggestive of an absolute elimination of the occurrence of any adverse event. This is not realistic for any pharmacovigilance system. A PV system can only limit or reduce harm resulting in an optimum risk benefit for therapy. Proposed change (if any): replace “preventing” with “limit” or “reduce”
Lines 133-134		Comment: As not all persons within organization are involved in and support the pharmacovigilance system, this sentence should be reworded. Proposed change (if any): Revise text to “All persons within organization should be trained, how and where information about product safety concerns gathered by them, should be reported.” Or “All personnel involved in the performance of pharmacovigilance activities shall be provided with appropriate instructions on critical processes, including business continuity…” in line with the text in line 180.
Line 231		Comment: The use of the word “effective” is subjective and not measureable. What would be “effective” versus not “effective” in an inspection scenario? Proposed change (if any): Revise text to read “Ongoing communication with competent authorities”, rather than “effective communication with competent authorities”.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 238		Comment: The use of the word “appropriate” is subjective and not measureable. What would be “appropriate” versus not “appropriate” in an inspection scenario? Proposed change (if any): Revise text to read: “communication of relevant safety information reaches HCPs and patients”, rather than “appropriate communication of relevant safety information.”
Line 240		Comment: Competent authorities quality system process should also identify duplicate submission of the same case ,from different sources (e.g. from MAH and patient) Proposed change (if any): Add this activity to the list.
Line 255		Comment: Current wording referencing “all documents” implies that draft and other non-binding documents should also be maintained within record management system. Proposed change (if any): Replace: “….should be maintained for all documents” with should be maintained for all essential documents related to critical PV activities (I.B.11.3)” or with “should be maintained for all individual case safety report source documents, and all final documents related to safety surveillance…..”
Lines 280-281		Comment: In addition to protecting records form destruction, measures should be in place to enable recovery of pharmacovigilance records / data in case of catastrophic events.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): Text should be amended to reflect this – '...to ensure that pharmacovigilance data and records are protected from destruction and enable recovery of pharmacovigilance data in case of catastrophic events.'
Line 306		Comment: There is a mistake regarding follow-audits Proposed change (if any): Change to "follow-up audits" instead of "follow-audits"
Lines 313-314		Comment: The requirement regarding "records created as a result of the pharmacovigilance process demonstrate that **ALL** steps required by the defined procedures have been taken" is extreme, as it is not feasible to produce records demonstrating that all required steps have been taken. It would be more meaningful and feasible to require documentation of **key** steps in the process. Proposed change (if any): "records created as a result of pharmacovigilance processes which demonstrate that ~~all steps required by~~ the defined procedures have been ~~taken~~ conducted"
Lines 318-321		Comment: We recommend a statement should be added to require that "root cause" for deviations/audit observations are established (with appropriate supporting CAPAs to address root cause). Proposed change (if any): Revise current text to read: "...that deficiencies and deviations from the established quality system are monitored, the root cause for such deviations are established, that appropriate supporting corrective and

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		preventative actions have been taken to address the root cause and that the actions taken have been verified".
Line 466		Comment: The statement: "A contact person at national level can also act as the QPPV" requires clarification. This could be misinterpreted that the national contact person is another 'local QPPV' or that they should be a back-up to the EU QPPV. Proposed changes (if any): Revise text to reach: "The QPPV may also act as a contact person at the national level."
Lines 492-494		Comment: The MAH should be responsible for assurance that appropriate corrective actions are implemented. Also providing the QPPV with copies of all CAPAs for all PV audits seems would be enormous undertaking for large companies conducting audits of multiple affiliates and marketing partners on a regular basis. The QPPV should be provided with only information relating to critical observations and the respective CAPAs for them. Proposed change (if any): Revise text accordingly. "...should provide the QPPV with information on critical observations and CAPAs following each audit, and the MAH shall ensure appropriate corrective actions are implemented."
Line 549		Comment: QPPV should be involved in review and approval of protocols for post authorisation safety studies not 'sign off' Proposed change (if any): Amend text accordingly: '...being involved in the review and ~~sign-off~~ approval of protocols for post-authorisation safety studies;'

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 585-586		Comment: This section states monitoring the use of terminology. 'Terminology' is too vague. Standard coding dictionaries (e.g. MedDRA) may more accurately describe the data entry of adverse events using MedDRA as required for process for ICSR. Proposed change (if any): Suggest replacing 'terminology' with "standard coding dictionaries (e.g. MedDRA)"
Line 590 (similar to 255)		Comment: The word "documents" is too broad in this line (Like in line 255) Proposed change (if any): Revise to read "... and <u>essential, final</u> documents relating . . .

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	(1) Where appropriate, it may be of benefit to make reference to the relevance of MedDRA to pharmacovigilance systems, in light of the EMA requirements for the use of this terminology. (2) The timely updating of respective medical terminologies with the most current version may also merit addition to the responsibilities of the applicant and marketing authorization holder in the EU.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
193-197		**Comment:** The addition of “coding terminologies” would complement the other examples of important pharmacovigilance skills and subject areas which necessitate the training of pharmacovigilance professionals. **Proposed change:** 193 Adequate training should also be considered by the organisation for those staff members to whom no 194 specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may 195 have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities 196 include but are not limited to those related to clinical trials, technical product complaints, medical 197 information, coding terminologies, sales and marketing, regulatory affairs, legal affairs and audits.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
Medicines and Healthcare Products Regulatory Agency

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

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E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	This GVP tends to have a lot of repetition in it. It also seems to duplicate some of what is said in other GVPs and then refers to them rather than concentrating on the quality system aspect.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
120-121		Comment: Should there be any reference to specials included in this section?	
306		Comment: This should read follow-up audits rather than follow-audits. Proposed change (if any):	
326		More detail may be needed here to clarify exactly what is meant by documenting “resource management”. If I am an MAH what do I actually need to do to fulfil this requirement?	
327		It would be useful to include responsibilities of those conducting pharmacovigilance activities, not just the managers and supervisors.	
361		Comment: ..Pharmacovigilance and **product** quality defect systems should be considered rather than quality defect systems	
364		Is the expectation that this would cover the issuing of a Dear Healthcare Professional Letter? If so it may be useful to state this as an example and other relevant examples to help MAHs understand what they should include in a procedure.	
373-375		Comment: Consideration should be given to business continuity plans in terms of proportionate risk assessment, i.e. number of reactions seen for a product	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
398		Comment: the last part of the sentence could be omitted as it does not add to the understanding. (which is covered by the quality system)	
405 – 409		Comment: Consideration should be given to amending the wording to: As a consequence of the monitoring and audit activities, which includes the pharmacovigilance system, corrective and preventative actions should be implemented when deemed necessary. These Plans should be reviewed to ensure that the actions have been completed.	
416-419		Comment: Does this fit in this section?	
437		Comment: Perhaps need to include something to indicate what this means in practice. Consider: "under these circumstances the PSMF should clearly state what products this system covers".	
444		Comment: Which GVP is this covered in – missing reference.	
463-466		Comment: Consider the change of reporting to the QPPV to …"who would be responsible for alerting the QPPV to any contacts with the Competent Authorities" The next sentence could then be removed.	
523 – 525		Comment: Consideration should be given to training of the QPPV in the company's products.	
528		Comment: Do you mean that the QPPV is an actual physical individual as opposed to a number of persons?	
573 & 574		Comment: Line 573 could be re-worded so that the QPPV is made aware of only those validation failures that are deemed	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		to affect pharmacovigilance outputs. Also, line 574 could be re-worded to “The QPPV should also be informed of changes to the database that could have an impact on pharmacovigilance activities”. Proposed change (if any):	
587 & 590		Comment: Is the paragraph starting on line 587 needed given what is stated in the paragraph starting on line 590? What happens when the system in the PSMF does not exist but the authorisation still does? Which retention period takes precedence in that situation given that the same type of documents could apply to both paragraphs? Proposed change (if any): Delete the paragraph starting on line 587 as this may cause confusion.	
606-7		Comment: consideration should be given to the documentation as being Full and complete as opposed to complete.	
813 & 815		As per the comment relating to 587, line 813 could be deleted as this may make the retention period for documents clearer. Having the additional paragraph on line 813 may cause confusion.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Version date: 21 May 2012 18:11:00

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
Alcon Inc. Novartis Consumer Health Novartis Pharma AG Novartis Vaccines & Diagnostics Sandoz Pharmaceuticals

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Novartis considers the module very well written providing a clear framework for the PV quality system.

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')*
74 - 75		Comment: Novartis notes that the ISO 9000 standards have been selected as the underlying tenet for this module in contrast to ICH Q10 which has been widely adopted by the pharmaceutical industry. This already establishes a different operating philosophy. In the Q&A it would be interesting to understand why ISO 9000 was adopted over the more modern ICH Q10. Proposed change (if any): none
190 -192		Comment: Novartis assumes that development plans would be the generic ones developed for the role and not individual personalised plans, the sharing of which will be constrained by both data privacy and local law. Proposed change (if any): none
202 - 206		Comment: Facilities and Equipment: It would assist greatly in understanding the scope of this requirement if examples of facilities or equipment were provided. Proposed change (if any): If a change of text is not possible a Q&A on this topic including examples would assist in the scoping of the requirement.
207 - 210		Comment: If EU wide standards against which the risk assessments for facilities and equipment should be conducted are available please could these also be included in a Q&A on the topic of facilities and equipment. Proposed change (if any): none
504		Comment: The extent of involvement of the QPPV in the due diligence knowledge sharing for operational

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		pharmacovigilance is very variable and often limited. The process for assessment of the potential partners Pharmacovigilance system can be achieved in other ways. Novartis suggests that due diligence is deleted from the sentence and replaced with the following. Proposed change (if any): …the QPPV should be assured that an overall quality system is in place ensuring the acquired companies/partners can conform to the MAHs Pharmacovigilance System.
577 - 578		Comment: Further clarification is required as to what is considered adequate documentation of delegation of QPPV responsibilities. For example is the delegation of QPPV responsibilities through SOP training documentation adequate, or are signed delegation forms required, or must it be clearly stated in the Pharmacovigilance System Master File? Proposed change (if any): Please provide further clarification on which EU QPPV responsibilities may be delegated

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16th April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
OPTUMInsight Inc.

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
176-178		Comment: Could GVP propose methodology for assessing that a 'sufficient number' of competent and appropriately qualified and trained personnel are available? The interpretation of this requirement is unclear, both when negotiating resource within an organisation and when preparing for future inspections. Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
86		Comment: medicinal products and detect any change to their risk-benefit balance Proposed change (if any): medicinal products and detect any change to their benefit- risk balance please consider this throughout the whole document
276 - 279		Comment: The processing of personal data may be justified if identifiable health data are processed only when necessary and only when the parties involved assess the necessity at every stage of the pharmacovigilance process [IM Art 15(2), Art 20(2)]. Question: Does any follow up measure require a new assessment of necessity by all involved parties? Please provide examples how to comply with this requirement. Proposed change (if any):
304 - 305		performance indicators where they are used to continuously monitor the good performance of pharmacovigilance activities [IM Art 11(1)]; Comment: detailed definition of performance indicators with examples is required
311 - 312		methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfil the quality objectives; comment: please provide examples
326		their resource management [IM Art 13(4)]; 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')*
		their human resources management [IM Art 13(4)];
594 - 596		To this end, the marketing authorisation holder shall continuously check the European medicines web-portal for any relevant updates, including consultations and notifications of procedures [IM Art 14(1)(e)]. Comment: Please provide a web link to prevent the MAH from being required to screen the whole website

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
Procter & Gamble

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Clarify the difference between Quality System and PV System throughout this document

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 5 – section I.B.4		Comment: Change the order of importance – safety should be before legal requirements Proposed change (if any): □ preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; □ complying with the legal requirements for pharmacovigilance tasks and responsibilities;
Page 6 – line 155		Comment: For clarity change managerial staff to management – throughout the document Proposed change (if any): management should be responsible for:
Page 8 – line 222		Comment: Insert “to” before patients Proposed change (if any): all information on the risks of medicinal products as regards to patients’ or public health, including
Page 10 – line 293		Comment: the term “quality objectives” appears 3 times in one sentence Proposed change (if any): rewrite
Page 10 – line		Comment: clarify what resource documentation is

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
326		Proposed change (if any):
Page 12 – line 391		Comment: For clarity change managerial staff to management – throughout the document Proposed change (if any):
Page 14 – line 463		Comment: Please provide a list of the countries that require a local QP for PV to be appointed Proposed change (if any): further information requested
Page 14 – line 487		Comment: For clarity change managerial staff to management – throughout the document Proposed change (if any):
Page 15 – line 492		Comment: For clarity change managerial staff to management – throughout the document Proposed change (if any):
Page 15 – lines 502 to 504		Comment: for the following sentence - When a marketing authorisation holder intends to expand its product portfolio, for example, by acquisition of another company or by purchasing individual products from another marketing authorisation holder, the QPPV should be notified early in the due diligence process in order – this is not always possible due to confidentialities Proposed change (if any): consider revising the text
Page 15 – line		Comment: - what is a natural person

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
528		Proposed change (if any): clarification
Page 17 – line 585		Comment: add “the before this sentence Proposed change (if any): the monitoring of the use of terminology, with data entry staff being instructed in the use of terminology
Page 18 – line 618		Comment: add “to ensure” to this sentence Proposed change (if any): holder to another organisation, the marketing authorisation holder shall retain responsibility to ensure that an
Page 18 – line 625		Comment: add ”the” Proposed change (if any): included in the pharmacovigilance system master file (PSMF) [IM Art 4(1)(f)] and a list of the contractual
Page 22 – line 800		Comment: remove “for” from the end of the sentence Proposed change (if any): and the Agency shall put in place the following additional specific quality system processes:

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 Apr 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 103-107		Comment: To avoid redundancy, the general provisions of the PV system and organization as described in the PSMF should not have to be described separately in SOPs as well. Proposed change (if any): Replace first sentence with: “The PV system master file should be an integral procedural part of the quality system”. ….
Lines 132 - 133		Comment: The sentence: “All persons within the organisation should be involved in and support the Pharmacovigilance system on the basis of task ownership and responsibility”, is confusing since not all employees have tasks related to Pharmacovigilance”. Proposed change (if any): Replace text with: All persons should be trained in forwarding suspected ADR which are being reported to them as company representatives.
Line 141-143		Comment: Although good cooperation with all stakeholders is highly advisable, the advantage of stating this in a regulatory guideline on quality systems seems questionable, as not measurable. Furthermore, it is not clear what "learned societies" is referring to. Proposed change (if any): Remove the paragraph.
Line 190		Comment:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		With the current text, we are concerned that inspectors may expect mini examinations in every single standard operation procedure. Currently many companies have exams documented with training certificates in key processes such as data entry, signal detection and MedDRA coding. It is important to highlight that many standard operation procedures cannot be memorised instead they must be consulted when the tasks, are being performed. Proposed change (if any): Limit the scope of competency examination to the selected critical competencies. It is suggested to add the following line. Before line 190: There must be a process for ensuring that all employees are trained in all relevant tasks, in addition there should be a process for identification of critical procedures for, which the knowledge and understanding gained after training should be tested. Line 190 should then be modified as follows: For these critical procedures there should be…….
Line 192		Comment: We assume that the professional development plans are not personalized but role specific
Line 202-206		Comment: It would help if examples for equipment are given
Line 254		Comment: We fear that with the current text the marketing Association holder may be expected to retain even draft documents and internal discussions. Proposed change (if any): Replace: “….should be maintained for all documents” with should be maintained for all essential documents

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		related to critical PV activities (I.B.11.3)" or with "should be maintained for all individual case safety report source documents, and all final documents related to safety surveillance…..."
Line 312-313		Comment: "Records created as a result of Pharmacovigilance processes which demonstrate that **all** steps required by the defined process have been taken …" The amount of documentation needed will be unreasonable high, if all steps should be documented **every time**. The focus should be on the job and not on the control. It should be documented that all steps have been conducted e.g. by signature, but not all steps should be signed off every time. In addition it is not every time a process is run e.g. safety surveillance that all steps are taken, it depends on the data, situation etc. Proposed change (if any): Suggest removing the last words, the sentence will read as follows: "Records created which demonstrate that the defined pharmacovigilance process has been conducted."
Line 492		Comment: For a big company with hundreds of affiliates and partners being audited and inspected regularly, the documentation which the QPPV have to review should be limited to a minimum. Proposed change (if any): Replace "A copy of the corrective and preventive action plan with": "A list of critical and major findings, findings with corrective and preventive action plans".
571-573		Comment: We agree that the QPPV should be aware of the validation status of the database, however, we are concerned that it will add unnecessary burden to the QPPV to be informed of any failure during the validation and the corrective actions that have been take.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Delete ",including any failure that occurred during the validation and the corrective actions that have been taken to address the failures."
Line 584		Comment: We have concerns regarding the documentation needed to demonstrate that data entry staff has been tested in the understanding of the use of various terminologies. Proposed change (if any): Replaced with: "Data entry staff must be instructed and examined in the use of the database. Furthermore, staff performing MedDRA coding must be trained in their proficiency verified.
Lines 589-591		Comment: Our concern is not about the retention time of 10 years, our concern is the scope of pharmacovigilance data and documents related to the authorities as medicinal product. Proposed change (if any): Replace "…pharmacovigilance data and documents relating to authorised medicinal products…." with "…..all essential documents related to critical PV activities (see I.B.11.3)….", or with "……all individual case safety report source documents, all final documents related to safety surveillance, labelling updates and product recalls…."

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
SciencePharma

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Could you please precise the process which should be in place within organization in order to check that training results and conduct of pharmacovigilance activities are in line with agreed professional development plans (v191-193). What kind of process should it be, who would assess whether the process is adequate?
	Could you please specify how risk assessment described in v 207-208 should be documented?
	Could you please specify if managerial and supervisory staff mean manager of pharmacovigilance/medical department or rather management board of the company (v 327)?
	Could you please explain if according to v 470 are there any other persons (apart from the QPPV) who should be authorized to introduce changes to PSMF
	Does “basic medical training” described in v 516 means the training for physicians (medical doctors)?

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	In general the guidance as written in this GVP module is very detailed. It should be kept in mind that MAH often have databases for regulatory affairs and also complainthandling which are validated and have an audit trail. However, this does not mean that for changes in such a system “controlled documents” are available on every change. This is the same for the audit trail / controlled changes for the PSMF, which would mean that several times a day a controlled document would need to be be updated when there is a change in one of the appendices. The quality system should guarantee the quality of reports and data as well as the quality and uniformity of pharmacovigilance processes. It should not turn into a purely out to be a bureaucratic exercise where several administrative assistants are only printing and tracking documents. In our view, the current proposals do not meet the primary objectives of the new legislation i.e. “simplification” and “reducing bureaucracy”.

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')*
62-66		Comment: 'The definition of a pharmacovigilance system is provided in Article 1 of Directive 2001/83/EC as a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance. The Agency likewise maintains a pharmacovigilance system to fulfil its pharmacovigilance activities.' Proposed change (if any): Amend for readability. 'The definition of a pharmacovigilance system is provided in Article 1 of Directive 2001/83/EC as a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX. *The pharmacovigilance system is* designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance. The Agency likewise maintains a pharmacovigilance system to fulfil its pharmacovigilance activities.'
122-124		Comment: It is not the quality objective of pharmacovigilance to promote the "effective" use of medicinal products. Propose: "Promoting the safe ~~and effective~~ use of medicinal products, in particular through providing ….."
142-144		Comment: There is no legal basis for the sentence with special regard to cooperation with patients or healthcare professionals. Therefore we consider this statement to be too vague/general and not appropriate for a

	Guidance on a legal text. Propose – deleted the last bullet. ~~Good cooperation should be fostered between marketing authorisation holders, competent authorities, public health organisations…..~~
180-181	Comment: 'All personnel involved in the performance of pharmacovigilance activities shall be provided with appropriate instructions on critical processes, including business continuity [IM Art 13(3), Art 18(3)].' There are two comments on this section. Firstly in general all employees of a MAH play a role in the performance of pharmacovigilance processes and they should be appropriately trained. For the so called first receivers (i.e. sales reps, med info RA, legal etc) there is definitely no need to be aware of and trained in business continuity. Their initial contact for internally reporting adverse events should be available. Secondly for the easiness of reading, the critical processes can be referred to the appropriate section. Proposed change: Line 180 and 181 should be replaced by: "All personnel possibly involved in initially receiving adverse events should be appropriately trained in the processes they have to conduct. All personnel involved in the further collating, assessing and reporting and further pharmacovigilance processes should be appropriately trained and receive instructions on critical processes (see I.B.11.3), including business continuity [IM Art 13(3), Art 18(3)]."
186 - 189	Comment: It is stated that the training for "all" personnel should support continuous improvement of skills, application of scientific progress and professional development. These training goals are not relevant to all Pharmacovigilance personnel. Training should be tailored to the particular role personnel undertake in pharmacovigilance activities. Proposed change: The training should, *where relevant*, support continuous improvement of relevant skills, the application of

	scientific progress and professional development. *The training should further* ~~and~~ ensure all staff members have *or gain* the appropriate qualifications *and* understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities.
191-193	Comment: 'There should be a process in place within the organisation to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, and in line with agreed professional development plans.' Proposed change (if any): Amend for readability. 'There should be a process in place within the organisation to check that training results at the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, are ~~and~~ in line with agreed professional development plans.'
203-210	Comment: A perfect quality system and perfect pharmacovigilance can be organised independent from facilities and equipment. It can be operated from airplanes, hotel rooms, shared offices etc in either handwriting or telephone or computerised system. Location, design, construction, maintenance are thereforeirrelevant and should not be prescribed in EMA guidance. Proposal: This section should be rewritten in a way that is less prescriptive. Location of and equipment used in the system should be taken into account in the business continiuity program.
216-220	Comment: '...shall follow-up such information, as appropriate, independent of its source, including information spontaneously reported by patients or healthcare professionals, published in medical literature, or arising in the context of a post-authorisation study.' Information from literature should not be followed up by the MA holder. Case reports in literature are in general well documented. Follow up requests for literature is an unnecessary burden to the author and does not increase the safety for the patients. The word "as appropriate" in this sentence is not enough. In serious emerging new safety issues it will be part of standard pharmacovigilance to get as much

	information as needed from all sources. Therefore the part on literature should be deleted from this paragraph. Proposal: "…. shall follow-up such information, as appropriate, independent of its source, including information spontaneously reported by patients or healthcare professionals, ~~published in medical literature,~~ or arising in the context of a post-authorisation study
243-244	Comment: There is no requirement for a quality system for to ensure that <u>follow up</u> is conducted by the competent authorities of any information as appropriate as reported to them from any source, including spontaneous reports from HCP and patients. This is not in line with the intentions of the legislation. Furthermore if MS receive cases for products for which the MA holder is required to do additional follow up, questionnaires or tests it should be the responsibility of the MS to forthwith notify the MA holders so appropriate actions can be taken. Proposal – change bullet one: Ensure the evaluation and submission of the quality, including completeness of pharmacovigilance data *received from spontaneous sources whereby the MS shall follow up such information as appropriate, independent of its source and ensuring the cases*. Add bullet: *The MS receiving spontaneous adverse events from all sources on product event combinations under close surveillance with the need to conduct additional pharmacovigilance activities should forthwith inform the MA holder so the appropriate actions can be taken according to the risk management plan of the product.*
263-265	Comment: 'the retention of documents relating to the pharmacovigilance systems and the conduct of pharmacovigilance for individual medicinal products, in accordance with the applicable retention periods.' Unclear what 'applicable retention periods' are at this stage of the Module. Would suggest a link to section I.C.1.4. where it states 'the retention of pharmacovigilance data and documents relating to authorised medicinal products as long as the marketing authorisation exists and for at least further 10 years after the

	marketing authorisation has ceased to exist [IM Art 15(4)];'
315 - 317	Comment: "…records and reports relating to the facilities and equipment including functionality checks, qualification and validation activities which demonstrate that all steps required by the applicable requirements, protocols and procedures have been taken." Proposed change (if any): examples could be given focussed on business continuity.
346	Comment: The bullets in this section describe the complete pharmacovigilance process – it does not make sense to define parts as critical when there are no non-critical processes.
373 - 375	Comment: 'back-up systems for urgent exchange of information within an organisation, amongst organisations sharing pharmacovigilance tasks or between marketing authorisation holders and competent authorities...' There is no need for such a backup system for interaction with authorities and other MAH, and the requirement therefore introduces bureaucracy, complication and is money and resources intensive. If there is an urgent exchange of safety information needed through the contract and through the pages on the agency's webportal for every MA holder contact details are available to contact the company. A second backup system therefore is not needed. Proposed change (if any): Delete the requirement
438 - 442	Comment: A PSMF is developed today usually not only for one MAH but a number of MAHs belonging to the same corporate group. Proposed change (if any): It should be clarified that affiliated MAHs belonging to the same corporate group can combine into one

	PSMF.
450-455	Comment: The QPPV is notified in the initial MA application. The name of the QPPV is maintained in the EVPRM database, is detailed in the PSMF and is available in the Eudravigilance database under QPPV details. These three systems should be enough to enable the MS and the agency to contact/find the relevant QPPV. To additionally require variations for QPPV and PSMF to be submitted, the objectives of the EU legislation are missed. It adds bureaucracy and increases costs at both MAH and CA level. Proposed redraft of these lines. The Marketing Authorisation Holder shall submit the name and the contact details of the QPPV as well as the location of the PSMF to the competent authorities in Member States and the Agency at the time of the submission of the application. The Marketing Authorisation Holder shall have an updated PSMF with these up-to-date information and shall submit relevant changes both to the EVPRM as well as to the Eudravigilance database.
457	Comment: 'Information relating to the QPPV shall be included in the pharmacovigilance systems master file (PSMF) [IM Art 4(1)(a)] (see Module II).' These requirements are described in Module II. There is no need to repeat them in this module Proposed change: Delete
492-494	Comment and proposed change to align with lines 489-490 and to ensure the QPPV gets all information as required: 'The managerial staff should provide the QPPV with a copy of the corrective and preventive action plan following each audit in the EU or relevant to the EU, so that the QPPV can *be* assure*d* that appropriate corrective actions are implemented.'
507-509	Comment: Due diligence; In this situation the QPPV should be made aware of the sections of the contractual arrangements that relate….. to request amendments

	The QPPV should be involved in drafting the pharmacovigilance parts so no amendments are needed in a later stage Proposal: In this situation the QPPV should, where possible, be ~~made aware of~~ *involved in determining* the sections of the contractual arrangements that relate….. to request amendments
549	Comment: “The QPPV should be involved in the review and sign-off of protocols of post-authorisation safety studies;” There is no need for the QPPV to be involved in and to sign off all PASS studies. Proposed change (if any): The QPPV should be involved in the review ~~and sign-off~~ of protocols of post-authorisation safety *studies conducted in the context of an approved EU RMP*
557 – 559 560 - 561	Comment: “Ensuring a full and prompt response to any request from the competent authorities in Members States and from the Agency for the provision of additional information necessary for the evaluation of the benefits and risks of a medicinal product’ ‘providing any other information relevant to the benefit-risk evaluation to the competent authorities in Members States and the Agency;” The above suggests that the QPPV could be seen as the only point of contact for all efficacy information which would normally go through regulatory affairs and other relevant departments . These sentences should be changed to indicate the QPPV is not responsible for RA/medical/clinical. Proposed change (if any): “Ensuring a full and prompt response to any relevant request from the competent authorities in Members States and from the Agency for the provision of additional information necessary for the evaluation of the safety part of the benefits and risks of a medicinal product’ ‘providing any other relevant safety information relevant to the benefit-risk evaluation to the competent

	authorities in Members States and the Agency;"
572 - 574	Comment: '…including any failures that occurred during validation and the corrective actions that have been taken to address the failures' A QPPV is not a specialist in validation. The QPPV should know that the system is validated. Only validated systems can be used for pharmacovigilance systems. What happens during the development of a system is not the task of the QPPV. Proposed change (if any): ~~including any failures that occurred during validation and the corrective actions that have been taken to address the failures'~~
585-586	Comment: 'monitoring the use of terminology, with data entry staff being instructed in the use of terminology and their proficiency verified [IM Art 15(3)]' This sentence should be clarified Proposed change (if any):
593-597	Comment: '…including the assessments and recommendations made public via the European medicines web-portal. To this end, the marketing authorisation holder shall…' Proposed change (if any): " European medicines" to "European Medicines Agency Website" or the "Agency" Website. The European Medicines Agency is already defined as 'the Agency'.
608-609	Comment: '…the marketing authorisation holders shall define the duties of the QPPV in a job description'. This is redundant in light of line 456

	Proposed change (if any): Either delete here or line 456.
630-633	Comment: “When preparing contractual arrangements, the MAH….. together with for example, agreed definitions, tools, assignments and timelines.” To avoid endless listings of definitions it is highly recommended to refer to annex I in the GVP. To avoid misunderstanding the sentence can be clarified Proposed change: When preparing contractual arrangements, the MAH….. together with for example, the reference *used* for agreed definitions, tools, assignments and timelines.
665-657	Comment: ‘To facilitate the interaction between competent authorities in Member States, the Agency, marketing authorisation holders and person reporting pharmacovigilance information, contact points shall be established [IM Art 18(1)].’ How and where are these contact details going to published?
686 - 687	Proposal: Replace “one Member states” by singular “Member State”
743	Comment: ‘monitoring **selected** medical literature for reports of suspected adverse reactions…’ How will MAHs access this data for literature potentially on their products? It is not clear in this Module nor in Module VI how suspected adverse reactions will be filtered down to MAHs, so how MAHs should access them (if there is even a need). The process of literature searching needs to be clear with a list of what publication sites will be checked, for what products, how often etc.

Please add more rows if needed.

<18 April 2012>

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

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

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

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

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1. General comments

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

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 74-75		Comment: Reference is made to ISO 9000. The version should be mentioned as there is some difference in the ISO 9000:2000 compared to the one from 2005 and when there are changes to the ISO 9000 norm this will not automatically change the GVP guidance Proposed change (if any): "...general principles of the ISO 9000:2005 Standards on..."
Lines 83-84		Comment: A PV system is not only existent to fulfil the legal tasks. A pharmaceutical manufacturer follows his ethical and moral obligations and the values of his company's philosophy. Proposed change (if any): Therefore it would be adequate to say "... to fulfil its legal tasks and internal standards and responsibilities..."
Lines 103-107		Comment: ISO 9000 is a companywide approach as a basic understanding by the management how to create a quality driven structure and processes – therefore the QA system is not an integral part of the PV-system but vice versa. Proposed change (if any): The pharmacovigilance quality system shall be an integral part of the ~~pharmacovigilance~~ company's entire quality system...
Line 117		Comment:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		These are not overall quality objectives but legal requirements. Quality objectives may also be process related for example translation activities, medical assessment etc. Proposed change (if any): The ~~overall quality~~ main legal objectives of a pharmacovigilance system are:
Line 126		Comment: see comment for line 117 Proposed change (if any): With the aim to fulfil the ~~overall quality~~ main legal objectives in...
Line 132		Comment: Not all persons in an organisation are involved in PV work therefore the wording should be …. Proposed change (if any): All persons within the organisation should ~~be involved in and~~ support the pharmacovigilance...
Lines 206-208		Comment: There should be a reference on the concept of risk assessment to be done like defined in GAMP5 when talking about equipment like databases or software applications.
Lines 253 - 280		Comment: It should be considered that the process of electronic record handling becomes more and more relevant also with regard to the new media in use. The controlled transfer of records into electronic documents should allow to destroy the paper based documentation – this should be explicitly defined in this section.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): Add specific chapter
334-335		Comment: This requirement is out of the legal scope as defined by the regulation or the directive and should be deleted.
343-344		Comment: It is understood that this refers to the organisation of the authority – otherwise this requirement is out of the legal scope as defined by the regulation or the directive and should be deleted.
Lines 383-384		Comment: This process is out of the entire control of the MAH and may therefore not be part of his PV QA system. Proposed change (if any): Delete the complete bullet point.

Please add more rows if needed.

17 April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
399		"The audits shall be conducted by individuals who have **no direct involvement in or responsibilities** for the matter or processes being audited". How should this be interpreted? A different department or company?
513		The QPPV should have skills for the management of PV as well as expertise or access to expertise in relevant areas such as medicine, pharmaceutical sciences **as well as epidemiology and biostatistics.** For small or generic companies who have products with a well established safety profile in their port folio, this requirement seems too extensive.
549		"being involved in the review and sign-off of protocols of post-authorisation safety studies" Comment: QPPV can sign off PASS and PEAS, but being involved in review of all protocols of post-authorisation studies is not feasible as such studies will be initiated by other departments or partners. Also, involvement in the review if the medicinal product will be used within the terms of the SPC, seems redundant. QPPV should be aware and receive AEs on a regular basis. Proposed change: delete the requirement.
590		Retention of PV data…as long as the MA exists and for at least further **10 years after the MA has ceased to exist.** Does this mean that the requirement for "indefinite" retention of PV data no longer applies?

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module I – Pharmacovigilance systems and their quality systems' (EMA/541760/2011)

Comments from:

Name of organisation or individual
Zeincro Hellas S.A.

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 104-108		Comment: It must be clarified that throughout the document the reference to the "quality system" always means the "quality system of a pharmacovigilance system" as defined in the Annex I – Definitions. Proposed change (if any): To be added in line 108 at the end of the paragraph: "To the rest of the document the term "quality system" always refers to the quality system of a pharmacovigilance system."
Line 118		Comment: In accordance with lines 80-81 and the use of modal verb "should", we consider the use of "should" to this sentence. Proposed change (if any): "The overall quality objectives of a pharmacovigilance system ~~are~~should be:"
Line 132		Comment: It is specified that "all staff members" should be motivated by higher management in relation to the quality objectives. We consider this is not applicable for all staff members (e.g. there are micro or small – sized enterprises where part time cleaning personnel and part time accountants are employed and such motivation seem to be superfluous). A rephrasing is proposed to reflect corresponding phrasing in lines 146-147. Proposed change (if any): "motivation for all persons involved in the relevant processes, ~~staff members~~ in relation to the quality objectives."
Line 135		Comment: The word "with" must be changed to "within" so as to refer to persons within the organisation. Persons involved **with** the organisation are a wider population and it is not always considered relevant to engage them in continuous quality improvement following the quality cycle in I.B.3.. Proposed change (if any): "All persons involved ~~with~~ within the organization"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 186-196		Comment: Provisions for training of personnel has to be clarified, as the references to the personnel in I.B.7. are confusing. For example, staff members referred to in line 187 has to be clarified that it concerns personnel involved in the performance of pharmacovigilance activities. Reference to the training for the rest of staff members are specified in lines 194-196 and therefore the “All staff members [...] safety concern” sentence in lines 189-190 may result to confusion. Proposed change (if any): Lines 186-189: “The training of the personnel involved in the performance of pharmacovigilance activities should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that pharmacovigilance ~~staff members~~personnel have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities.” Please clarify and relocate (if necessary) the provision in lines 189-190. In case it is referred to the personnel involved in the performance of pharmacovigilance activities please replace the phrase “All staff members” in line 189 with the phrase “Personnel involved in the performance of pharmacovigilance activities” or “Personnel involved”. In case the “All staff members” provision in lines 189-190 refers to all personnel of the organisation, then please move the sentence from lines 189-190 to the end of the last paragraph (i.e. in line 198).
Lines 231-235		Comment: Verb is missing to this bullet point to clarify what shall be ensured. Proposed change (if any): Line 231: effective communication flow with competent authorities is established, including communication on new or changed risks […], the pharmacovigilance system master file […], risk management systems […], risk minimisation~~s~~ measures […], periodic safety update reports […], corrective and preventive actions […], and post-authorisation safety studies […];

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 238-239		Comment: Verb is missing to this bullet point to clarify what shall be ensured. Proposed change (if any): ~~appropriate communication of~~ relevant safety information is appropriately communicated to healthcare professionals and patients
Lines 330-332		Comment: There is a danger for misunderstanding if the sentence is interpreted as: their arrangements for record management for the documentation of the pharmacovigilance system including its quality system as well as for pharmacovigilance data and documents (i.e. other than pharmacovigilance documents) relating to authorised medicinal products, including the location of the records [Art 15(5)]. Proposed change (if any): "their arrangements for record management for the documentation of the pharmacovigilance system including its quality system as well as for pharmacovigilance data ~~and~~ /documents relating to authorised medicinal products, including the location of the records [IM Art 15(5)]."
Line 357-358		Comment: Assessment of PSURs is performed by competent authorities, therefore a clarification is considered appropriate as not to imply that appropriate instructions shall be in place by the marketing authorisation holders for the assessment of PSURs. Proposed change (if any): "submission and assessment (if applicable) of periodic safety update reports;"
Line 449		Comment: In Volume 9A (page 24, 2.2.3.b) the QPPV is referred to as the EEA QPPV. In addition, the terms EU QPPV and EEA QPPV are both used by marketing authorisation holders. The use of the parenthesis: (QPPV) after the EU acronym in line 449 may lead to the use of the term EU QPPV. In case this is not promoted, we consider a clarification inside the parenthesis to be appropriate. Proposed change (if any): "the EU (referred to as the QPPV)"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 450-451		Comment: It might be comprehended that the marketing authorisation holder shall submit the name and contact details of the QPPV to the competent authorities of all Member States and not solely to Member States where it holds marketing authorisation(s). Proposed change (if any): “The marketing authorisation holder shall submit the name and contact details of the QPPV to the competent authorities in Member States and the Agency (as applicable)”
Lines 495-501		Comment: Provisions for a procedure to ensure the QPPV is able to obtain information from the adverse reaction database at any time might prove to be very difficult to be implemented by micro or small-sized enterprises. This may require purchasing of advanced databases and the need to use database specialists as mentioned; this is considered to be onerous and irrelevant for many of these enterprises that collect only a limited number of cases. Proposed change (if any): Line 498: “information from the competent authorities or the Agency, ~~at any time~~within a reasonable timeframe, as agree with the authorities on a case by case basis. If this procedure requires the”
Line 528		Comment: In accordance to the previous comment for line 449 we consider the use of the parenthesis: (QPPV) after the EU acronym in line 528 may lead to the use of the term EU QPPV. In case this is not promoted, we consider a clarification inside the parenthesis to be appropriate. Proposed change (if any): “in the EU (referred to as the QPPV)”
Lines 608-609		Comment: Provision for a job description for the QPPV is already described in line 456. Proposed change (if any): We propose lines 608-609 to be omitted.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 847-849		Comment: Delegation of pharmacovigilance tasks from one Member State to another Member State may result to a Member State become extremely influential to certain pharmacovigilance tasks, in cases when a lot of Member States would delegate the same task to the same Member State. We propose to limit the number of Member States for which a Member State can undertake a specific pharmacovigilance task. The number of the Member States proposed below is indicative and can be further discussed with stakeholders. Proposed change (if any): "A competent authority in a Member State may delegate any pharmacovigilance task to another Member State subject to a written agreement of the latter Member State [DIR Art 103]. Each Member State may undertake a specific delegated pharmacovigilance task for no more than two other Member States. The written agreement should be reflected by exchange of letters, defining the scope of the delegation."
Lines 850-853		Comment: We consider that only transfer of pharmacovigilance tasks from a competent authority in a Member State to another competent authority in a Member State is appropriate. A competent authority shall not transfer pharmacovigilance tasks to an organisation (e.g. a CRO). Proposed change (if any): "A competent authority in a Member State may transfer any or all of the pharmacovigilance tasks to another competent authority in a Member State~~organisation~~, but the ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system always remains with the competent authority in a Member State."