EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2012
EMA/428821/2012
Patient Health Protection

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

GVP Module II – Pharmacovigilance system master file

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.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8668
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
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16/APR/2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

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

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

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

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

1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 105		Comment: Regarding the elements that shall include the PS, it is included a "proof that the applicant has at his disposal a qualified person responsible for Pharmacovigilance". Proposed change (if any): Could you confirm if the proof could be a letter or email with the notification to NCA of name of QPPV?
257 to 259		Comment: the list of tasks delegated by the QPPV and people responsible for them could be subject to changes too frequently to be kept in a specific document.
286 to 288		Comment: The list of contracts and agreements related to the fulfilment of pharmacovigilance obligations could have multiple changes on a daily basis making the continuous update of the PSMF very difficult. This requirement seems to be contrary to the nature and objectives of the new PV legislation. Proposed change: There could be SOP's in place that will maintain these agreements. The content of this list would be regularly updated by the QPPV or a designed responsible.
382 to 384		Comment: Please, clarify targets for the performance of the PV system and the performance indicators that must be provided.
416 to 425		Comment: The pharmacovigilance system master file should also contain a note associated with any audit where significant findings are raised. This means that the presence of findings that fulfil the EU criteria for major or critical findings will be indicated in the list of audits conducted, and the corrective and preventative action plan (with deadlines for completion) for these findings will be summarized. A reference to the full audit

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***
		report and corrective and preventative plan document(s) should also be provided. Proposed change: This information is sensible data for the company. Additionally, it is already included in the audit reports which are already available for the Competent Authorities. The corrective and preventative actions are included too in the Company Audit Reports. Hence, MAHs consider that this activity is not feasible and a reference to the location of the audit report should be enough.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
AESGP

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Both the Regulation and the Directive are aiming for increased patients safety, reduction of bureaucracy and enhanced transparency. In parts the proposed module seems to miss those aims as it generates multiple requirements for storage and maintenance of essentially similar data without adding to patient safety or transparency. It is recommended to reduce the required dataset to the absolute minimum to enable the focus on improving patient safety and transparency whilst reducing replicated bureaucracy. 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 finalised and that the final document is not expected to be published before May-June 2012, this makes the commenting on this draft module more difficult. The PSMF is a very comprehensive document differing considerably from the previous DDPS and is applicable from July 2012. The Guidance document however will be available only shortly before this date. According to the transitional provision it could be the case that after receiving a renewal for a MA a MAH has to have in place the PSMF immediately after July 2012. Or a company might wish to submit an application for a MA shortly after July 2012. Therefore, an additional transitional arrangement should be established to allow the preparation of a correct and complete PSMF. We suggest to allow for 9 months for the implementation of the PSMF as there have to be major updates made in current processes and be summarised in the PSMF. This is particularly true for the supply of lists. In addition, the EC Q&A on transitional arrangements specifies that MAH may introduce on a voluntary basis a pharmacovigilance system master file at an earlier stage in the period between July 2012 and 2015 via the filing of a variation. However there is no guidance available as to the type of variation that would normally be required. In addition nationally approved products are not in scope of the Variations regulation up to now. In order to reduce the administrative burden on both the industry and the regulators it would be helpful if the transitional arrangements could provide additional guidance on the most efficient and pragmatic way of moving from a DDPS to the PSMF for those companies that do not want to phase in the PSMF on a product by product basis. The structure and organisation of companies might differ considerably and as a consequence the PSMFs will also differ substantially. Therefore, a common template for the PSMF seems neither appropriate nor desirable.

Stakeholder number *(To be completed by the Agency)*	General comment
	In general, this module frequently contains the same information in different sections, which makes it difficult to read. In order to avoid such duplications the text should be rearranged, streamlined and more clearly structured.

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')*
110-111		Proposed change: Please add a new line after line 110: *"A reference to the PSMF registry number / QP registry number would be adequate"*.
114-117 **MAJOR**		Comment: The need to file a variation in case of changes to the summary of the Pharmacovigilance system is adding an unnecessary bureaucratic burden in light of the fact that the location of the PSMF and the name and contact details of the QPPV are required to be submitted to EVMPD in accordance with Article 57, as stated in lines 608-611. Therefore, it is suggested that individual product variations should not be necessary and this requirement be removed. Proposed change: The mention of the need for a variation needs to be removed from the following lines: 114-117 131-132 148-154 567-569
117-119		Comment: the waiver to provide pharmacovigilance system summary for traditional herbal medicinal products is appreciated. Proposed change: none – keep unchanged
172-174 (173)		Comment: The QPPV should explicitly accept the following changes in writing: - inclusion of products into the pharmacovigilance system for which the QPPV is responsible; If this requirement holds on both the EEA level and the product level (i.e. each new strength, form of administration etc.) this may be quite cumbersome and administrative. It would be less administrative if this requirement referred to the active moiety level ("active moiety" instead of "products"). It is understood that the QPPV will have oversight on all products by cooperation with both the regulatory affairs groups and third parties. The QPPV should also be informed if she/he is no longer responsible for a product. Line 173 should be changed

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		in "inclusion of active moiety into or deletion of active moiety from the pharmacovigilance system for which the QPPV is responsible;"
297-298 **MAJOR**		Comment: Copies of agreements should not be part of the PSMF because this contravenes the key concept that the PSMF should be succinct (as described in II.B.6 in line 516) and presents duplication of information located elsewhere with the MAH. At present this also represents a conflict with lines 458 of this GVP module which refers to a list of contracts. With regards to this please also see the principle comment to section II.B.4.8. (line 430). A list detailing where agreements are in place should be provided and the actual agreements available on request. Proposed change: please remove the need to include signed copies of the contracts in the PMF.
309-319		Comment: We believe that the request to include and maintain a current list of all studies, registries, and surveillance or support programmes does not add value to the PSMF as most of this information is either known through approval procedures with the authorities and/or is presented in detail in the respective periodic safety update reports provided to the authorities on a regular basis as long as relevant safety information results from such sources. The PSMF provides sufficient detail that MAHs have systems and processes in place to collate and collect safety reports from all sources relevant to their products and it does not add any value to maintain a highly administrative list of current studies, registries, surveillance support programmes and of their respective status as requested in this section. In addition there are no globally accepted clear definitions of what constitutes a surveillance or support programme or what is considered to be a non-interventional study. This would hence result in significant inconsistencies and different interpretations. This requirement therefore seems to be contrary to the stated objectives of the revised PV legislation – those of simplification and reduction of duplication and administrative burden. It is acknowledged that the MAH has the responsibility to ensure that ICSRs from all sources have to be captured and analysed as outlined in the other GVP modules and these processes are sufficiently displayed by referencing SOPs and contractual agreements. Proposed change: Therefore, to avoid unnecessary duplication of efforts, and ensure adequate use of resources it is suggested to delete lines 309 to line 319 completely or to indicate a location where the references can be made available.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
340		Proposed change: We suggest qualifying "a description of the processes" as "a short/succinct/concise description of the processes" to clarify here that e.g. SOPs would not be expected to be reproduced in this section.
363-365		Comment: In line 363 "a table listing all pharmacovigilance related procedural documents" is required. This list seems to be appropriate to demonstrate that **all** applicable processes are addressed adequately by SOPs. We propose to present this list in the Annex of the PSMF. Proposed change: please add: "this table may be provided as an annex to the PSMF".
376-377		Comment: the meaning of 'latest figures' is unclear. Proposed change: please amend text to say: "an overview of the timeliness of PSUR reporting to competent authorities in EU over the past year"
383-385		Comment: Line 383 states that "A list of performance indicators *must* be provided" however lines 383-384 refers to the Annex to the PSMF [IM Art 4(2), Art 11] reading "where applicable, a list of performance indicators…..". This is repeated in the section covering the Annex contents themselves (Line 463). Therefore, it seems even from this GVP module that a list is NOT mandatory. It's also inappropriate for a guidance to use 'must' which is a binding term. Proposed change: The sentence "A list of performance indicators *must* be provided" appears to be inaccurate and should be deleted.
391-396		Comment: This list seems redundant with that required in line 363. We refer to our comments under line 363. Proposed change: delete sentence and cross refer to line 363-365.
399-400		Comment: As in smaller companies in particular one individual may have more than one role it is suggested that resource management may also be captured as full time equivalents (FTEs). The information should be limited to staff having pharmacovigilance function.

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		Proposed change: The organisational chart giving number of people or FTEs involved in pharmacovigilance activities.
404		Comment/Proposed change: According to Module I line 302 the wording should be changed in "instruction on critical pharmacovigilance processes". This does not seem clarified in the current revised draft version of the IM published on the commission's website (http://ec.europa.eu/enterprise/tbt/tbt_repository/EU29_EN_1_1.pdf. we understand that this term refers to the areas listed below line 370, i.e., ICSR reporting, PSUR reporting, safety variation submissions and fulfilment of commitments, other obligations and conditions.
419		Comment and proposal: From our point of view it is sufficient to include critical findings from the audits into the PSMF. Therefore, "major or" should be deleted.
429		Comment and proposal: In line with module I "pharmacovigilance systems and their quality systems", the item "quality system" should be used instead of quality management system.
432-443		Comment: The main part of the list should be available from EVMPD anyway. Duplicate data collection and maintenance is an unnecessary administrative burden and source of mistakes. It would be beneficial to both authorities and companies to be able to refer to data available on EVMPD and not present the data in addition as a copy in the PSMF Annex. Proposal: It is recommended to update the list at least once a month unless a new active moiety needs to be included.
434		Comment: The list of substances should include the INN of the active substance. However, for herbal or homoeopathic active ingredients no INN exists. How should these substances be named? In the same way as on the label? The naming of the substances should be consistent with the information to be transmitted to EMA according to Art 57 (2) of the regulation (EC) No. 726/2004.
430-471		Comment: In addition, as the nature of the information provided by the sources described in II.B.4.8 is such that it can change frequently, maintaining a continuously updated version of the information in the PSMF is

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		duplicative. Pulling such a breadth of detailed and constantly changing information from a multitude of sources into the PSMF also introduces significant potential for disconnect. It is therefore proposed that regular reports from respective systems are maintained in the PSMF for QPPV and MAH oversight purposes, but that up-to-date ad hoc reports are provided from the controlled system in the event of a 7 day/immediate request from a regulatory authority. Proposal: Add additional text: Where content of PSMF Annex changes frequently e.g. product list, it is acceptable to maintain regular reports from respective systems for QPPV and MAH oversight however up-to-date ad hoc reports should be provided from the controlled system in the event of a 7 day/immediate request from a competent authority.
444		Comment:The list of medicinal products should be organised per active substance. This is appropriate for products with a single active ingredient only. Combination medicines contain more than one active ingredient and one active substance might be used is several different products. Therefore, the order of the products should be decided and justified by the MAH and should be comprehensible.
463		Comment: We feel that the requirement for audit history over the preceding 10 years is not practical or relevant, due to changes in legislation and practices over such an extended time period. The revised version of the IM referred to the fact that the master file should contain a logbook recording any alteration of its content within the last five years. This logbook should record the date, the responsible person and where appropriate the reason for the alteration. Proposed change: We suggest a 3 year history of audits would be appropriate. This is motivated by the fact that most inspectorates in the EU only go back three years.
472-512		Comment: As the PSMF is not routinely submitted to competent authorities there is no mechanism for them to be aware of changes other than QPPV details or location of PSMF. It is unclear therefore what could be the trigger for them to solicit information. Authorities have anyway the possibility to request for the PSMF. Notification should in any cases remain voluntary. Proposed change: Amend text to say: MAHs may notify competent authorities about important changes to the

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		pharmacovigilance system.
484-485		The PSMF as described in this module including the annexes would be constantly changing which would be quite impractical to work with. To enable change control, the addition of the following sentence is recommended: <u>The frequency of updating any parts the PSMF itself as well as the annexed documents should be determined internally following a risk-based approach and documented in the PSMF.</u>
484-492		Comment: For those components of the PSMF that derive information from company controlled systems that are validated and have an associated audit trail, the source of the history of change should be derived from the controlled system and not be duplicated in the PSMF. Proposed change: Insert new sentence after first sentence – <u>Where the list content is derived from a controlled system then the history of change may also be derived from the controlled system.</u>
519-522		Comment: The legislation states that the PSMF has to be provided within 7 days from request of the Authorities. The notion of "immediate providing" is contrary to the legislation, not feasible in practice. Proposed change: please clarify that "immediately providing" cannot be shorter than 7 days.
541-573		Comment: The information in this section is only a repetition of information given in the sections above. Therefore II.C.1.1 could be deleted completely.
561-566		Comment: The information in the two sentences of this paragraph is redundant.
Minor/editorial comments		
68		Comment: Need a possessive 's after (QPPV) Proposed change (if any): Add 's
113		Comment: Change "not longer applicable" to "no longer applicable" Proposed change (if any): change not to no
250		Comment: this should be a bullet point Proposed change (if any): make this sentence a bullet point

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376		Comment: "to" missing Proposed change (if any): insert "to" before "competent authorities

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17th April 2012

Submission of comments on GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
AstraZeneca

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

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 II – Pharmacovigilance system master file' (EMA/816573/2011) AstraZeneca has had the opportunity to contribute to the EfPIA comments and agree to. Additionally, AstraZeneca would like to provide some further comments which follows below as general and specific comments.
	The content of the PSMF should be fully in accordance with that specified within the finalised implementing measure i.e. there should be no additional requirements over and above that specified in the final implementing measure. For example, noting that there is no cross-reference to a specific IM article, thereby implying that the implementing measure on the PSMF does not contain a requirement for a 'current list of studies', then this should not be specified within this GVP module and the requirement currently proposed in lines 309-319 should be deleted. It is clear from the transitional arrangements that a PSMF is required for any new MAA after 02 July for CAP and 21 July for all other routes of authorisation and for all renewals due after these dates. Other regulatory applications such as major line extensions, referrals, Type II variations should not trigger a requirement to submit a PSMF unless directly related to the DDPS or PSMF. Regulatory applications already submitted and under review at the time of entry into force of the regulation should not require the retrospective submission of the PSMF. Under the current variations legislation, grouping does not include National licences. Therefore a switch from DDPS to PSMF for all products/procedures at the same time will entail the same level of complexity as we currently see for managing DDPS variations. It would be helpful if transitional arrangements could be put into place to facilitate grouping. Variations will only be required for changes to the PSMF Summary Description (e.g. QPPV details or a Master file location), in accordance with the variations regulation. Variations will not be required for changes to the PSMF itself. The term "variation" should not be used to describe changes made within the PSMF itself, this is covered by the logbook. The XEVMPD will be updated with information (detail to be defined) on Safety-related variations and PSMF Summary Description variations. The term "variation" should not be used to describe updates to the XEVMPD.

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')*
108-109		**Comment:** Given the accountabilities assigned to the QPPV, the statement signed by the applicant as part of the Summary of the Pharmacovigilance System should also be signed by the QPPV, given its very fundamental nature. **Proposed change (if any):** a statement signed by the applicant and QPPV to the effect that..."
128 and 572		**Comment:** Details regarding location of PSMF and QPPV details – "Any change to the location shall be notified immediately to the Agency in order to have the information in the database.... and on the .....web-portal updated" It should be clear that this means that the database and web-portal are updated (by the appropriate means), and not that there is a requirement to formally notify the agency (e.g. by signed statement or letter) as this would be duplicative of the variations procedure. **Proposed change (if any):** Any change to the location shall be notified immediately to the Agency *by updating the database (EVMPD)*.....
172-174		**Comment:** The list of items that the QPPV should explicitly accept in writing should also include the following: **Proposed change (if any):** Add: "transfer of significant services for pharmacovigilance to a third party e.g. outsourcing of PSURs"
381		**Comment:** The PSMF should include a description of the monitoring methods applied and contain as a minimum: where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of marketing authorisation(s) relevant to pharmacovigilance. **Proposed change (if any):** More clarity is needed on what is in scope of "commitments", "obligations" or "conditions".
496-497		**Comment:** Extensive, significant or important descriptive changes to the content of the master file may necessitate a new version of the pharmacovigilance system master file to be produced, and these should be recorded in the logbook… **Proposed change (if any):** More clarity is needed on what constitutes extensive, significant or important descriptive changes to go into logbook, as opposed to what can be tracked in history of changes (line 490-491).

Please add more rows if needed.

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Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

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

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

1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
117-119		Comment: *Holders of registrations of traditional herbal medicinal products might be subject to PV-inspections as well as any marketing authorisation holder. Moreover, safety monitoring for these products is relying solely on proper signal detection processes. Proof of existence of a pharmacovigilance system and contact details of the QPPV should be supplied upon registration of these products.* Proposed change (if any): *Delete phrase.*

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

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

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Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	There are instances where the guidance adds requirements to those already stated in the Directives and Regulations. This places an additional burden on the MAH and it is not clear if this would lead to greater compliance. The guidance is more prescriptive which means that it does not allow room for the MAH to risk adapt their processes to be compliant with the Directive & Regulations. This more prescriptive approach of the guidance, is restrictive and not helpful in allowing the MAH adopt a process which best fits their circumstances and which creates the best environment for 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')*
53		Comment: Please explain what this means – "There is no requirement for variations for changes in the content of the pharmacovigilance system master file." Does it mean that there is no need for a submission of a variation to the regulatory authorities for changes in the content of the pharmacovigilance system master file? Proposed change (if any): There is no requirement for *submission of* variations *to the regulatory authorities* for changes in the content of the pharmacovigilance system master file.
165		Comment: The Directive & Regulations do not state where any CAPA plans are to be located and the MAH should be allowed flexibility about this, in order to adapt it to their particular circumstances. Proposed change (if any): The types of changes that should be routinely and promptly notified to the QPPV are: □ the ~~addition~~ *creation* of corrective and/or preventative action *plans* ~~to the pharmacovigilance system master file~~ ~~(e.g.~~ following audits and inspections~~)~~ and managed deviations from the processes defined in the quality management system for pharmacovigilance;
409		Comment: There is a considerable burden by requiring MAH to continuously update the SMF . We propose that this list be periodically updated. Proposed change (if any): Information about quality assurance auditing of the pharmacovigilance system should be included in the pharmacovigilance system master file. A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism should be provided, with a *periodically updated* list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex referred to II.B.4.8. [IM Art 4(2), Art 8(1)]. This *periodically updated* list should describe the date(s), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces relevant to the fulfilment of the obligations in the Directive 2001/83/EC.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
417		Comment: The guidance should exactly reflect the wording of Directive 2010/84/EC Article 104 put forward by the legislator. The regulators used the wording in the Directive to assist the MAH to comply with the requirements. There is no need for additions not mentioned in the Directive. Proposed change (if any): ~~The pharmacovigilance system master file should also contain a note associated with any audit where significant findings are raised. This means that the presence of findings that fulfil the EU criteria for major or critical findings will be indicated in the list of audits conducted, and the corrective and preventative action plan (with deadlines for completion) for these findings will be summarised. A reference to the full audit report and corrective and preventative plan document(s) should also be provided. The note and associated corrective and preventative action(s), as well as reference to the location of the audit report shall be documented in the pharmacovigilance system master file until the corrective and/or preventative actions have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified [Dir Art 104(2), IM Art 8(2)].~~ ~~As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the pharmacovigilance system master file should also describe the process for recording, managing and resolving deviations from the quality management system.~~ *"The marketing authorisation holder shall perform a regular audit of his pharmacovigilance system. He shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed. "*
431		Comment: Line 431 states that all below "shall" be contained in the annexe when some of the items are not requirements of the Directive or Regulation. Proposed change (if any): An annex to the pharmacovigilance system master file ~~shall~~ should contain the following 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')*
463		Comment: "An annex to the pharmacovigilance system master file shall contain the following documents: ….. □ A list of all completed audits, for a period of ten years, and a list of audit schedules [IM Art 8(1)]." The guidance states that this "shall" be provided, but only quotes the Implementing consultation [IM Art 8(1)] which does not state this. Proposed change (if any): ~~A list of all completed audits, for a period of ten years, and~~ A list of audit schedules *indicating which audits were completed* .
494		Comment: As the PV master file has to be controlled would you please confirm that the CAPA section related to audits will not be routinely asked for during an inspection and can be kept separate by QA. Proposed change (if any):

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
Bayer HealthCare

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Many implementation details of the PSMF are currently still under consultation. Therefore, to facilitate the transition to the new PSMF a “grace period” should be considered whereby a company has the opportunity to add the PSMF reference during the review period with day 121. A DDPS submitted e.g. in the first quarter after July 2 would thus not represent a formal ground for invalidation of the dossier if a letter of commitment is provided that the PSMF reference is added at day 121.

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')*
192		"… shared by several marketing authorisation holders…" Proposed change: "shared by several marketing authorisation holders, not part of the same parent company,"
297 - 300		In keeping with the concept of the PSMF being a concise summary document for overview and cross-reference, we suggest to provide copies of signed agreements <u>on request</u>, i.e. consistent with requirements for other contracts (line 294-296). Proposed change: "Individual contractual agreements *and the list provided in the Annexes (see II.B.4.8.)* shall be made available at the request of national competent authorities and the Agency or during inspection and audit [IM Art 7(3)] ~~and the list provided in the Annexes (see II.B.4.8.)~~. *This specifically concerns* ~~The pharmacovigilance system master file should also contain copies of signed~~ agreements for significant delegated activities, such as: • pharmacovigilance service provision (QPPV, safety data entry, PSUR writing, electronic ICSR reporting, evaluation of safety data, etc.); • delegation concerning the pharmacovigilance system master file.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

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

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

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

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

1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
51		Comment: For new licence applications it is clear that we need to submit a summary of the applicant's PV system and cross refer to the PSMF. It is not entirely clear what needs to be done for existing licences in July. Clearer guidance is required
101		Comment: If the summary in the dossier is amended how is the change to be handled? Will a variation be needed? Will a special variation category be given?
103		Comment: For new licence applications it is clear that a summary of the applicants PV system needs to be submitted and cross reference made to the PSMF. It is not clear what needs to be done for existing MAs in July – what is the transition arrangement? What type of submission will be needed for the PSMF?
116		Comment: When will details of variation type etc be available for changes to the summary document?
117		Comment: Specifically what is implied by traditional herbal medicinal products?
126		Comment: This section mentions the PSMF will be registered on the database linked to Article 57 – how will this be managed?
133		Comment: Location and QPPV change requires variation – how will this be handled? Costs could be considerable depending on size of the company.
141		Comment: Mentions that the PSMF will be registered on the database linked to Article 57 – how will this be managed as there is no mention of it in the information so far?
172 - 173		Comment: This could be a large task for a large company for the QPPV to accept new products in writing – is it acceptable to delegate?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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		Comment : The PSMF should be a global overview, but there are country specific systems, products etc. – how should this be managed?
236 - 239		Comment : What are “essential documents”? There is a statement that "The content of the PSMF should reflect global availability of safety information for medicinal products authorised in the EU. Not sure exactly what this means - is this actual core safety information for each INN, or a statement about how core safety information is developed and maintained, or is it summary data on what safety variations have been submitted in certain time period for each INN etc?
258		Comment: For QPPV delegated tasks, will individual names or job titles be required?
294 - 296		Comment: This statement suggests contractual agreements shall be made available upon request to the NCA - can commercially sensitive and financial information be removed? Protection of commercially sensitive information is considered to be an important matter for both the MAH and the contracted party
297		Comment: Where there are a number of local lists and agreements, how should this be managed for a large global country – should all the affiliate information also be included in the PSMF?
303		Comment: A description of global units handling ISCR collection should be included, including medical information sites, it is not clear if this means that every country affiliate with a local sales office (and therefore may receive ADRs) needs to be listed? Please clarify.
321		Comment: What databases should be included other then in PV-ie Medical information, PTC etc. Should this include affiliate databases?
333 - 365		Comment: II.B.4.5. it is not clear if you are a multinational company, does the PSMF need to include a list of all the affiliate local SOPs and systems as well as all corporate SOPs? If local SOP list needed, are SOPs of associated functions (e.g. regulatory) and any outsourced activities to be included as well?
346		Comment: Risk Management systems – how is it envisaged this will work for generic companies, where they are required to be in line with the innovator?
373-375		Comment: Is this compliance of PSUR etc to all CA in the world? For all metrics what period has to be included? One year? Two years?...

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
417		Comment: Does this mean that all audit findings from all local affiliates would need to be entered into the PSMF? Does this include internal audits? Does it just refer to audits of the PV systems, or other associated functions (e.g. medical information, regulatory?)
423 - 471		Comment: II.B.4.8. and II B.5: There seems to be a great amount of information included in the PSMF on marketing authorisation status that could change on a constant basis (e.g. marketing status in different countries, safety variation status, SOP lists) - will an update to the PSMF need to be submitted on each occasion? Also, it is not clear if,(for example) a regulatory database that tracks marketing status and variation submission/approval status could be cross referred to in the PSMF and these metrics be updated (say) quarterly, or if this information needs to be updated on a continuous basis with the scope of the PSMF? How will this work in practice?
458		Comment: Do all SDEAs have to be included (eg local, non-EU agreements) or just global SDEAs?
463		Comment: please confirm what type of audit schedules this refers to – it is not clear if this refers to corporate internal planned PV audits, or does this cover all internal audits at affiliate level of PV and related areas?
552		Comment: States that during a MAA application applicant may be asked to provide PSMF. Can the authority request changes as part of the MAA assessment?
612 - 614		Comment: This section suggests the QPPVs details and contact information will be made publicly available. This could leave the QPPV open to nuisance calls/contacts unrelated to PV enquiries. Proposed change (if any): Suggest that only the specific contact details for reporting issues/AEs to the company are made public.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

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).

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	In this draft Guideline on good pharmacovigilance practices (GVP) Module II - Pharmacovigilance System Master File very often "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.
	In general, this module frequently contains the same information in different sections, which makes it difficult to read. In order to avoid such duplications the text should be rearranged, streamlined and structured more clearly.
	The line-numbering is not the same comparing published document Module II under http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/landing/landing_page.jsp&mid=WC0b01ac05801b7e46 (here on page 2 line 36 + line 37) with published document Module II sent before (here on page 2 line 36). It could be a deviation of 1 line.
	The PSMF is a very comprehensive document differing considerably from the previous DDPS and is applicable from July 2012. The Guidance document however will be available only shortly before this date. According to the transitional provision it could be the case that after receiving a renewal for a MA a MAH has to have in place the PSMF immediately after July 2012. Or a company might whish to submit an application for a MA shortly after July 2012. Therefore, an additional transitional arrangement should be established to allow the preparation of a correct and complete PSMF.
	The creation and in particular the maintenance of the new PSMF will be a new workload which is not feasible and manageable and is therefore not acceptable for small and medium sized companies with a smaller amount of case reports. The currentness of all these appendices is pretty much time-consuming. The extent should be reduced, eg. II.B.4.8. (different appendices), II.B.4.3. (list of studies).
	The due date should be better outlined, at which time the MAH / applicant should have a PSMF in place. Text proposal:

Stakeholder number *(To be completed by the Agency)*	General comment
	"For new applications submitted after July 2012: If a new authorisation is applied for after July 2012 (2 July 2012 for centralised procedure, 21 July 2012 for all other procedured), a PSMF is required." For marketing authorisations already granted before 21 July 2012 (2 July 2012 for centralised procedures): It is confusing, that the uncorrected 2010/84* is available on the official websites, outlining MAs "granted before 21 July 2011" and a "period of 3 years starting from 21 July 2011" (instead of 2012 as corrected in the CORRIGENDA Corrigendum to Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use). *see http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf Text proposal: "For marketing authorisations already granted before 21 July 2012 (ie, 2 July 2012 for centralised procedure applications): A PSMF is required at least on 21 July 2015 (ie, 2 July 2015 for centralised procedure applications) or at the date on which the marketing authorisation is renewed, whichever is earlier."
	It is not understandable, why a MAH could not implement the PSMF and inform all EU-authorities, that by now the PSMF is in place and valid for all MAs of the MAH. This would be clear, simple and feasible. In practice, the MAH now has to keep both, the DDPS and the PSMF up to date and change DDPS to PSMF and PSMF summaries by variations. In the Question and answers document 163570 it is foreseen for already submitted applications, that applicants contact the competent authorities, which may agree "on a case-by-case basis". This is an extensive workload and not feasible.

Stakeholder number *(To be completed by the Agency)*	General comment
	Proposal: if a MAH has a PSMF in place, the MAH should inform all EU-authorities and the DDPS is not valid any more.
	The structure and organisation of companies might differ considerably and as a consequence the PSMFs will also differ substantially. Therefore, a common template for the PSMF seem not to be appropriate.
	In the Commission Implementing Regulation (EU) on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC is followed, the structure of the content as well as some details are not in accordance with the GVP Module II. For example the Commission Implementing Regulation (EU) on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC lists the bullet points for the content: (1) Information relating to the qualified person responsible for pharmacovigilance (2) A description of the organisational structure of the marketing authorisation holder, including the list of the site(s) where the pharmacovigilance activities are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorisation study management, and management of safety variations to product particulars. (3) A description of the location of, functionality of and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose. (4) A description of data handling, recording and the process (5) A description of the quality system for the performance of pharmacovigilance activities (6) Where applicable, a description of the activities and/or services delegated by the marketing authorisation holder relating to the fulfilment of pharmacovigilance obligations in accordance with Article 7(1). Whereas the GVP Module II lists as bullet points for content 7 points, in another order and with 7 points: II.B.4.1. PSMF section on qualified person responsible for pharmacovigilance (QPPV), II.B.4.2. PSMF section on the organisational

Stakeholder number *(To be completed by the Agency)*	General comment
	structure of the marketing authorisation holder, II.B.4.3. PSMF section on the sources of safety data, II.B.4.4. PSMF section on computerised systems and databases, II.B.4.5. PSMF section on processes, II.B.4.6. PSMF section on pharmacovigilance system performance, II.B.4.7. PSMF section on quality system, A comparison of the annexes shows, that the order and the points are the same, but the description of the points is not the same.
	All abbreviations should be explained in the text (e.g. there is no explanation for "IM"). Furthermore, all citations should be checked (like line 50 [IM Art 3(1)]) – citation does not fit to the corresponding 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')*
Line 100 - 119		**Comment**: It should be clarified that this refers to the EU-QPPV (and not to local QPPVs, eg. Stufenplanbeauftragte in Germany, if they are not EU-QPPV and do not have an oversight on the data outside of Germany).
Line 107 - 108		**Comment**: The statement signed by the applicant should be signed by both, the applicant **and** the QPPV. It is essential that the QPPV confirms to have the necessary means to fulfil the tasks and responsibilities
Line 113-116		**Comment**: "amendments…shall be submitted via a variation application…" **Proposed change (if any):** "amendments…shall be submitted in accordance…" [without variation]
Line 140 - 141		**Comment**: "Once the database ….is functional…" – what will be required in the time before this status is achieved?
Line 173		**Comment:** The QPPV should also be informed if she/he is no longer responsible for a product. Line 173 should be changed in *"inclusion of products into or deletion of products from the pharmacovigilance system for which the QPPV 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')*
		responsible;"
Line 189 - 191		**Comment:** How should "a QPPV" be understood? As one single person like in line 546? If yes, this should be clearly stated here. The headline of this section is "the representation of the pharmacovigilance system". The information given in line 189 – 191 however does not fit to this section and should therefore be included elsewhere.
Line 227		**Comment**: spelling error "is shared, is advised" **Proposed change (if any):** "is shared, it is advised"
Line 244 - 256		**Comment**: Directive states in Art.104(4) that "national competent authorities **may** request the nomination of a contact person for PV issues at national level" . But the guideline now states in II.B.4.1, that the PSMF **shall** include information relating to the contact person for PV where such a person has been nominated at national level. So this is more than originally requested in the Directive. **Proposed change (if any):** "shall" should be replaced by "may"
Line 267 - 318		**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')*
		Huge number of documents which are now to be included in the PSMF, and which have to be updated frequently (also local documents). Please also see general comment above (high workload, not feasible for smaller and bigger companies).
Line 286		**Comment**: "Links with other organisations… should be outlined." – how should this be in practice? The links are changing frequently. **Proposed change (if any):** "Information about links with other organisations … should be available on request"
Line 296 - 297		**Comment**: The PSMF should contain copies of signed agreements for significant delegated activities. Such agreement might be voluminous documents and therefore expand the PSMF considerably. For the reason of transparency a list of agreements including the topics covered should be sufficient instead of complete signed agreements. **Proposed change (if any):** "Signed agreements for significant…should be available on request."
Line 308-315		**Comment**: "…current list of studies" – not feasible in practice, since they are changing frequently **Proposed change (if any):** "…current list of studies… should be available on request.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 334 - 338		**Comment:** The item "the nature of the data held (e.g. the type of case data retained for ICSRs)" is not clearly defined. The nature of data retained depends on the nature of data received on a specific ICSR. It seems not appropriate to list all the potentially retained data in the PSMF.
Line 339 - 340		**Comment:** It is unclear how "a description of the processes" should be understood. If it is expected that full SOPs are to be included in this section this would not be acceptable. Furthermore, it must be considered that SOPs normally are written in the local language. A translation of all documents would be not feasible, especially for smaller companies.
Line 362 - 364		**Comment:** In line 363 "a table listing all pharmacovigilance related procedural documents" is required. This list seems to be appropriate to demonstrate that **all** applicable processes are addressed adequately by SOPs. We propose to present this list in the Annex of the PSMF.
Line 366 - 385		**Comment**: It is not clear which metrics are expected by the authorities (e. g. timelines) And shouldn't this be the duty of authority inspections, to evaluate the compliance with legal requirements?
Line 371		**Comment**: 90-day-reporting: will not yet be applicable for all countries. Proposed change (if any): The sentence in Line should be amended by "90-day reporting, where applicable":

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		"Figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting, where applicable over the past year."
Line 387 - 428		**Comments**: Requirements ("all major or critical findings, and the CAPA-Plan, and a reference to the full audit report"…) exceed the content of the EU-Directive, see Art.104(2): "He shall place a note concerning the main findings of the audit on the PSMF". **Proposed change (if any):** The obligatory requirements should be adapted to the EU-Directive (Art. 104(2)). **Comment:** In this section a list of documented procedures and processes including number, title and effective date is required. How is this list distinguished from the list required in line 363? Clarification is needed.
Line 403		**Comment:** According to Module I line 302 the wording should be changed in "instruction on critical **pharmacovigilance** processes".
Line 426 - 428		**Comment:** The item "quality management system" is not defined. If this should be a reference to module I "pharmacovigilance systems and their quality systems" than the item "quality system" should be used.
Line 417 - 419		**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')*
		From our point of view it is sufficient to include critical findings from the audits into the PSMF. Therefore, "major or" should be deleted.
Line 431 - 434		**Comment 1:** (1) In case only one PSMF exists in the company an annex which lists all medicinal products is redundant as this information is contained in the EVMPD which contains details about the location of the PSMF (line 126) / "A list of medicinal products" – not feasible and already provided for EU as Product Database. **Proposed change (if any):** "A list of substances is mandatory. A list of medicinal products … should be available on request" **Comment 2:** The list of substances should include the INN of the active substance. However, for herbal or homoeopathic active ingredients no INN exists. How should these substances be named? In the same way as on the label? The naming of the substances should be consistent with the information to be transmitted to EMA according to Art 57 (2) of the regulation (EC) No. 726/2004. **Comment 3:** Requirements ("shall contain…a list of all completed audits for a period of 10 years"…) exceed the content of EU-Directive **Proposed change (if any):** The obligatory requirements should be adapted to the EU-Directive.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 443 - 447		**Comment:** The list of medicinal products should be organised per active substance. This is appropriate for products with a single active ingredient only. Herbal or homoeopathic medicinal products often contain more than one active ingredient and one active substance might be used is several different products. Therefore, the order of the products should be decided and justified by the MAH and should be comprehensible.
Line 463 - 465		**Comment**: It is not clear what "performance indicators" are? This is redundant to line 383 (targets for the performance of the PhV) and line 373 (metrics to monitor the quality)
Line 468 and 497		**Comment:** The citation regarding Article 6(5) of the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC [IM Art 4(1) seems to be an error as there is no Article 6(5) available – maybe Article 6(4) was meant?
Line 471 - 511		**Comment**: Consequently to comments in II.B.4.7 (line 387 – 428) and II.B.4.8 (line 430 – 470): process/activities to implement change control systems to this extent are not feasible for small and middle sized companies
Line 483-488		**Comment**: see comment concerning 431-434
Line 489-499		**Comment:** How to document the history of changes and the logbook in a feasible way? Is it really mandatory to describe any changes?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): All versions should be archived. There is no need to document all changes in detail.
Line 540 ff		**Comment:** The information in this sections is only a repetition of information given in the sections above. Therefore II.C.1.1 could be deleted completely.
Line 560 - 565		**Comment**: In case section II.C.1.1 will not be deleted completely (see comment above): The information in the two sentences of this paragraph seem to be redundant.

<Date of submission>

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
Bristol Myers Squibb

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

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

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

1. General comments

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

2. **Specific comments on text**

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***
297-300 (IIB 4.2)		Comment: *Copies of signed agreements for significant delegated* activities should *be included in the PSMF* : the list includes PV service providers and is finished by a "etc…". Proposed change (if any): Stipulate that signed agreements for commercial arrangements are excluded. Provide an exhaustive list to avoid any misinterpretation.
302-319 (IIB 4.3)		Comment: *Sources of safety information should also include a current list of studies, registries, surveillance or support programmes sponsored by the MAH:* Please note the complexity of the requirement with an expected daily update of status for studies/organized programmes. Proposed change (if any): Can focus be on interventional and observational studies only and exclude the other programmes? Is there an alternative to expected daily update?
366-386		The section on PV performance mentions that the PSMF should contain evidence of ongoing monitoring. What is the date range for the overview of metrics that the MAHs are expected to provide?
401		A listing of sites where the personnel are located. Is this referencing EU or EEA?
404		Instruction on critical processes. Could this be clarified?
430-471		This PSMF section is referring to a lot of information which will be captured in the EVMPD. Are there plans, going forward, to extract information from EVMPD? Would you please clarify what the name of medicinal product stands for? Is it the tradename, the form and strength description or the pack size or only the tradename?

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***
		Would you please clarify if there is a need of products authorised in the EU or the EEA? The Rapporteur is mentioned on the PSMF. Is it the Rapporteur's country that is sufficient?
463 (IIB 4.8)		Comment: *A list of all completed audits, for a period of ten years, and a list of audit schedules*: Please confirm 10 years is fixed? Proposed change (if any): Can the 10 years be reduced to 5?
519-522 (IIB 6)		*Comment: Although provision of the document within 7 days of request by a competent authority is stated in the Article 23(4) of Directive 2001/83/EC, marketing authorization holders should be aware that immediate access to the pharmacovigilance system master file may also be required by the competent authorities*: Does it means that a copy of PSMF should be available in all Member States in case of a request of immediate access by a Competent Authority in EU?

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

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
	Celgene welcomes the opportunity to comment on the draft GVP module II and the fact that the DDPS will be replaced by the PSMF thus reducing the burden of frequent filing of variations just because of changes made to the DDPS. However, the switch from the DDPS to the PSMF should be possible for all products of one MAH at the same time, e.g. via a grouped variation. It would be a duplication of efforts to have to maintain both a DDPS and a PSMF until all necessary variations for all individual products have been filed and approved. Also, throughout the draft GVP module reference is made to the Implementing Regulation, however, it is not yet finalized.

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 47-49 & 121-124		Reference: Section II.A. Introduction "The pharmacovigilance system master file shall be located either at the site in the EU where the main PV activities or the MAH are performed or at the site where the QP operates." Comment: If the PSMF is in electronic format, maintained in an electronic medium, the QPPV has access does the aforementioned statement require the availability of a hard copy on site if the server is outside the EU? Proposed change (if any): An electronic format should be sufficient irrespective of the location of the server as long as the PSMF can be made available within the timelines foreseen per Directive 2001/83/EC and Regulation (EC) No 726/2004.
Lines 68-69 & 121-124		Reference: Section II.B. Structure and Process "…the PSMF location, must be within the EU." Comment: If the PSMF is maintained in an electronic format does this mean that the server in which the document resides must be in the EU? If yes, does a hybrid system in which the PSMF is maintained electronically but available in hard copy at the location of the QP in the EU satisfy this requirement? Proposed change (if any): An electronic format should be sufficient irrespective of the location of the server as long as the PSMF can be made available within the timelines foreseen per Directive 2001/83/EC and Regulation (EC) No 726/2004.
Lines 102-104/		Reference:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
110-111		"Article 8(3)(ia) of Directive 2001/83/EC requires a summary of the applicant's pharmacovigilance system to be included in the marketing authorisation application, which shall include the following elements: • a reference to the location where the pharmacovigilance system master file for the medicinal product is kept. " Comment: Additional transitional provisions would be required for those companies that file a marketing authorization application a renewal application shortly after 2nd July as the location of the PSMF needs to be specified in the filing which implies that the PSMF is in place then. However, as the final versions of the IM and the GVP module will only become available shortly before July 2nd, 2012 it is not feasible to have a PSMF in place that meets all the requirements Proposed change (if any): Transitional provisions should apply to filings submitted between July 2nd, 2012 and January 2nd, 2013.
Lines 159-160		Reference: Since a specific QPPV has responsibility for the pharmacovigilance system, changes to the pharmacovigilance system master file should also be notified to the QPPV in order to support their authority to make improvements to the system. Comment: GVP module I – Phamacovigilance systems and their quality systems mentions in section I.C.1.1. mentions that "The marketing authorisation holder should therefore ensure that the QPPV has access to the pharmacovigilance system master file (PSMF) as well as authority over it and is notified of any changes to it." Proposed change (if any): Change wording referenced above to: "Since a specific QPPV has responsibility for the pharmacovigilance system, **the QPPV has access to the pharmacovigilance system master file (PSMF) as well 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')*
		authority over it and changes to the pharmacovigilance system master file should also be notified to the QPPV in order to support their authority to make improvements to the system."
Lines 165 - 167		Reference: The types of changes that should be routinely and promptly notified to the QPPV are: • the addition of corrective and/or preventative actions to the pharmacovigilance system master file (e.g. following audits **and inspections**) and managed deviations from the processes defined in the quality management system for pharmacovigilance; Comment: There is no legal requirement to add corrective and/or preventative actions resulting from inspections to the pharmacovigilance system master file. This goes far beyond the requirements of the Directive, art. 104 (2). This kind of information should be available to both the QPPV and EMA/ the national competent authorities anyway and changes and to the PV system following inspection will also be reflected in the PSMF. Proposed change (if any): Remove **'and inspections'** from the sentence to read: "the addition of corrective and/or preventative actions to the pharmacovigilance system master file (e.g. following audits) and managed deviations from the processes defined in the quality management system for pharmacovigilance;"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 261-263		The details provided in relation to the QPPV should also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance (including registration with Eudravigilance). Comment : GVP module I – Phamacovigilance systems and their quality systems mentions in section I.C.1.2. That "If the QPPV has not completed basic medical training in accordance with Article 24 of Directive 2005/36/EC, access to a medically trained person (i.e. in accordance with Article 24 of Directive 2005/36/EC) shall be available [IM Art 13(1)] and this access should be documented in the pharmacovigilance system 518 master file (PSMF) (see Module II)." Proposed change (if any): This sentence from GVP module I – Phamacovigilance systems and their quality systems mentions in section I.C.1.2. should also be mentioned in GVP module II - Pharmacovigilance system master file, section II.B.4.1. subsequent to the sentence in lines 261-263.
Lines 291 – 292		Reference: " …service providers (e.g. medical information, auditors, patient support programme providers, study data management etc.), …" Comment: The activities performed by the example service providers given in the brackets are not pharmacovigilance obligations, hence inappropriate Proposed change (if any): Replace examples by service providers performing e.g. case management, expedited reporting, aggregate report preparation, signal detection etc.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 371 - 372		Reference: "…PSMF include a description of the monitoring methods applied and contain as a minimum: • an explanation of how the correct reporting of ICSRs is assessed. Figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting over the past year;" Comment: It should be clarified that this relates to the expedited reporting in the EU as these requirements do not apply globally. Proposed change (if any): Suggested wording: "Figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting **in the EU** over the past year;"
Lines 517		Reference: "… it must be possible to keep the information **continuously** up to date …" Comment: 'continuously' has been deleted from the current draft of the Implementing Regulation, hence is should be removed here. Proposed changes (if any): The sentence should read: " ...it must be possible to keep the information up to date…"
Lines 530 - 538		Reference: The pharmacovigilance system master file should be written in English (unless the marketing authorisation holder only holds approvals in one Member State when it can be written in the EU official language for that

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		territory), indexed in a manner consistent with the headings described in the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC [IM Art 4] and this guidance and allow easy navigation to the contents. Comment: The headings in the Concept Paper on the IM and in this module do not match and appear in different order, the final version of the IM is not yet available. Hence it is not quite clear how the PSMF should be indexed. Proposed changes (if any): It should be ensured that the headings in the final versions of the IM and this GVP module are consistent, otherwise the "**and**" in "...indexed in a manner consistent with the headings described in the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC [IM Art 4] and this guidance …" should be replaced by "**or**".

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
Chugai Pharma UK Ltd

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
II.A:Introduction:L48 The pharmacovigilance system master file shall be located either at the site in the EU where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site where the qualified person responsible for pharmacovigilance operates [IM Art 3(1)].		In II. L48. As to electronic archiving of PVMSF, can we consider that the PSMF is located at the site in the EU, in case that the EU affiliate can access the PVMSF, however, the server is located in US or in Japan?
II.B.2.3.:Registration:Once the database referred to in Article 57(1)(d) of Regulation (EC) No 726/2004 is functional, all pharmacovigilance system master files will be registered in EVMPD and a unique number assigned.		Once the database referred in Article 57 is functional, can a company outside of the EEA register the PSMF into the EVMPD?

Please add more rows if needed.

17.04.2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
CIS bio international/IBA

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

1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 406-407		Comment: Is it to be considered that each employee in the company might receive safety report? Proposed change (if any):
Lines 432-435		Comment: How to handle submitted renewals without notified answer from the Competent Authorities within the time limit? Proposed change (if any):

Please add more rows if needed.

<18 April 2012>

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

EFPIA – European Federation of Pharmaceutical Industries & Associations

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	EFPIA is supportive of the move from DDPS to PSMF and acknowledges and welcomes that some of the comments and recommendations made during the public consultation on the concept paper for the Implementing Measures have been incorporated in the GVP module. <u>Transitional Arrangements</u> It is clear from the transitional arrangements that a PSMF is required for any new MAA after 02 July for CAP and 21 July for all other routes of authorisation and for all renewals due after these dates. It is anticipated that many MAHs may not want to maintain both a PSMF and a DDPS in parallel and would therefore be looking for a way to move to PSMF for all products simultaneously. The Variations regulation allows for grouped variations however there is no guidance available as to what classification of variation that would be required and nationally approved products are not in scope. Neither the Transitional requirements nor the published guidelines include this situation and it would be very inefficient if all companies have to follow the unforeseen route to replace the DDPS with the PSMF. In order to reduce the administrative burden on both the industry and the regulators it would be helpful if the Transitional Arrangements could provide additional guidance on the most efficient way of moving from a DDPS to the PSMF for those companies that do not want to phase in the PSMF on a product by product basis. Additionally confirmation of the scope of "new" applications (e.g. MAA, licence renewal, referral) and whether this includes variations (e.g. line extensions) submitted between 2012 & 2015 would be helpful. For renewals, confirmation is also required that the implementation date refers to the submission (not expiry date) of licence renewal applications after the July 2012 deadline
	<u>Continuous update to PSMF</u> By far the most common and consistent comment from EFPIA members related to the requirement for the PSMF to be continuously updated. Members are unanimous in the view that this would place an unreasonable administrative burden on the

Stakeholder number *(To be completed by the Agency)*	General comment
	industry with no discernible benefit to patient safety. The required comprehensive content of the PSMF means that there could be multiple changes occurring on a daily basis making continuous update of the PSMF unfeasible. This requirement is completely contrary to the stated objectives of the revised PV legislation. To reduce the administrative burden on industry but to respect the spirit of the requirement, we recommend that the PSMF should be updated periodically, at a minimum quarterly, and the most up to date version of the PSMF provided upon request.
	<u>Content of the Annex</u> The Annex to the PSMF should be that part [of the PMSF] that contains those components which will be subject to continual updating. This includes those component which provide current status of contractual agreements, and studies/registries/surveillance or support programmes, a list of documented procedures and processes related to pharmacovigilance activities, as well as compliance monitoring and system performance information. This will facilitate the ongoing maintenance of the descriptive PSMF sections referenced in Module section II.B.4.1- II.B.4.7. However, the Module as currently drafted appears to require information that will be subject to continual updates to be included in section II.B.4.1- II.B.4.7., when they would be more appropriately housed in the Annex to the PSMF. Additionally the size and nature of the requirements means that there could be multiple changes occurring on a daily basis making continuous update of the PSMF practically impossible. As the information will typically be derived from controlled systems the requirement to hold the same information in two places is duplicative and resource intensive. This requirement therefore seems to be contrary to the stated objectives of the revised PV legislation – those of simplification and reduction of duplication and administrative burden. It should therefore be acceptable that the PSMF links to the controlled systems for up-to-date information and a regular report be generated and retained in the PSMF for QPPV and MAH oversight.
	<u>Scope of content of PSMF</u>

Stakeholder number *(To be completed by the Agency)*	General comment
	The content of the PSMF should be fully in accordance with that specified within the finalised implementing regulation i.e. there should be no additional requirements over and above that specified in the regulation. For example, noting that the current draft implementing regulation (articles 3 & 4) does not contain a requirement for a 'current list of studies' in the PSMF, this should not be specified within the GVP module and the requirement currently proposed in line 309 should be deleted.

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')*
105		Comment: In the DDPS, the CV of the QPPV fulfils this function. We propose that the same will satisfy this requirement in the PSMF Proposed change (if any): "proof *(for example via inclusion of a C.V.)* that the applicant....."
108-109		Given the accountabilities assigned to the QPPV, the statement signed by the applicant as part of the Summary of the Pharmacovigilance System should also be signed by the QPPV, given its very fundamental nature. Please amend to "...*signed by the applicant and QPPV to the effect that*..."
114-117		Comment: Retaining the need for a variation if changes to the summary of the PV system are made is inefficient and places a bureaucratic burden on both Regulators and the Industry. As this location of the PSMF and the name and contact details of the QPPV are required to be submitted to EVMPD in accordance with Article 57 it is suggested that individual product variations should not be necessary and this requirement be removed.
126-130		Comment:"*any change to the location shall be notified immediately to the agency*". This is not in line with the legal notice 57(2) which states immediately and no later than 15 calendar days. Proposed change (if any): "any change to the location shall be notified immediately and no later than within 15 calendar days to the agency"
143-147		Comment: More guidance is needed on the procedure for applying for the master file reference number. In particular, the following points should be clarified: (1) when the number should be applied for, relative to the marketing authorisation application ("at the time of marketing authorisation application" suggests this is part of or in parallel to the MAA); (2) whether the unique number is specific for the master file or the particular application – it would be preferable to have a unique number for the master file, as having different numbers associated with each product or application covered by the master file will add unnecessary complexity; (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')*
		whether the unique number will change during the lifecycle of the product (e.g. as new or additional products are added to the master file's scope) – it would seem preferable to have a unique number that does not change. Proposed change: Provide clarification in the module on the points raised above.
165		Comment: "*managed deviations from the processes defined in the quality management system for pharmacovigilance*." Most deviations are categorised into levels according to the criticality of the deviations. Suggest that only significant deviations need to be notified to the QPPV otherwise the QPPV will get inundated with minor (non-critical) deviations. Proposed change (if any): "*managed* ***significant*** *deviations from the processes defined*...."
172-174		This list of items that the QPPV should explicitly accept in writing should also include: • *transfer of significant services for pharmacovigilance to a third party e.g. outsourcing of PSURs*
177-201 and 286-295		Each PSMF will have a unique number assigned in XEVMPD. Please clarify if, for products where licensing agreements are in place, a MAH need to add other companies details or if will this be managed by the legal agreement.
192-202		Comment: Where the MAH has delegated part of or all of the pharmacovigilance activity for a product to e.g. a licensing partner or contractor, it is advised that the MAH may cross refer to all or part of the PSMF managed by the system of the party to whom the activity has been delegated. Since an individual contractor(s) may be a service provider, and not an MAH, it would not be possible to cross refer to their PSMF. The cross reference to the other parties PSMF is also subject to agreement on access to that system'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')*
		information for the MAH and authorities. The MAH is required to be able to assure the content of the referenced files(s) in relation to the PV system applicable to their product. As the PSMF is not product specific, the content of the PSMF will, in most cases, be considered confidential proprietary information to that MAH. Therefore the MAH will not be able assure the content of the referenced files from another MAH's PSMF. This assurance should instead be accomplished by auditing the licensing partner as per Monitoring of the performance and effectiveness of the PV system and its quality system I.B.12, Module I. Proposed change: Amend text to read: For a particular product(s) the marketing authorisation holder may delegate through written agreement (e.g. to a licensing partner) part or all of the pharmacovigilance activity for which the marketing authorisation holder is responsible. In this case the pharmacovigilance system master file of the marketing authorisation holder may cross refer to all or part of the pharmacovigilance system master file managed by the system of the party to whom the activity has been delegated.
197-201		In the following sentence, the requirement to cross refer is unclear: "In this case the pharmacovigilance system master file of the marketing authorisation holder may cross refer to all or part of the pharmacovigilance system master file managed by the system of the party to whom the activity has been delegated subject to agreement on access to that system's information for the marketing authorisation holder and the authorities." Recommendation: Indicate whether the "reference" needs to be by Company name or by the unique number assigned by EVMPD.
219 -225		This statement is not clear: "*When delegating any activities concerning the pharmacovigilance system and its master file, the marketing authorisation holder retains ultimate responsibility for the pharmacovigilance system, submission of information about the pharmacovigilance system master file location, maintenance of*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		the pharmacovigilance system master file and its provision to competent authorities upon request" this specifically refers to instances when the marketing authorization holder contracts these responsibilities externally to the MAH. For delegation of responsibilities within the MAH the detailed roles and responsibilities for the pharmacovigilance system master file content, submissions and management, and to govern the conduct of pharmacovigilance defined in the MAH's SOPs and procedures are considered sufficient." **Proposed change**: Revise to read: "*When delegating* ***to external third parties (i.e. those that are not part of the MAH's group of companies)*** *any activities concerning the pharmacovigilance system and its master file, the marketing authorisation holder retains ultimate responsibility for the pharmacovigilance system, submission of information about the pharmacovigilance system master file location, maintenance of the pharmacovigilance system master file and its provision to competent authorities upon request [IM Art 7(1)].* ***Detailed written agreements describing the roles and responsibilities for pharmacovigilance system master file content, submissions and management, as well as governance of the conduct of pharmacovigilance in accordance with the legal requirements, should be in place*** *[IM 226 Art 7]."*
228-233		Comment: Since licensing partnerships is generally product specific, accessibility of the pharmacovigilance system master file to all applicable MAHs may not be possible due to the nature of the confidential and proprietary information contained. Assurance that the pharmacovigilance system is appropriate and compliant should be accomplished by auditing the partner as per Monitoring of the performance and effectiveness of the PV system and its quality system I.B.12, Module I. Proposed change: Amend text to read: When a pharmacovigilance system is shared, it is advised that the partners agree on how to mutually maintain the relevant sections within their own pharmacovigilance system master files. Accessibility 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')*
		pharmacovigilance system master file to competent authorities should be defined in written agreements.
258-260		**Comment**: For large multinational companies with large portfolios, the EU QPPV may have many delegations in place which are documented in the company SOPs rather than via individual delegation agreements. The use of SOPs should be an acceptable mechanism to document formal delegations. **Proposed change**: Revise to read: "*A list of tasks that have been delegated by the qualified person for pharmacovigilance shall also be included in the annexes (See 11.B.4.8), and this should include a description of the activities that are delegated and to whom.* ***Where such delegations are described in Company SOPs, details of the SOP (number and title) may be used to describe the delegated functions.***"
279-280		Comment: Further guidance is requested to clarify the scope of 'pre-and post-authorisation study management'. It is unclear whether this relates to pharmacovigilance activities of study management or those related to clinical trial management of pre and post authorisation studies such as site management, monitoring, data management, statistics etc
287-296 303-308		**Comment**: These two sections require a list of license partners, contractors and agreements that may have significant overlap **Proposed change**: Revise to read: (Lines 303-308) "*The description of the main units for ICSR collection should include all parties responsible, on a global basis,*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		for solicited and spontaneous case collection for products authorised in the EU. This should include medical information sites as well as affiliate offices and may take the form of a list describing the country, nature of the activity and the product(s) (if the activity is product specific). Information about third parties (licence partners or local distribution/marketing arrangements) ***that may be the source of safety information should be indicated in the list required in II.B.4.8 and should be referenced in this section*** ~~***should also be included in the section describing contracts and agreements***~~ *(see II.B.4.2. and II.B.4.8.)."* A corresponding change should also be made to lines 287-296.
297 – 300		**Comment**: '*Significantly delegated activities*' should refer to significantly delegated pharmacovigilance activities. **Proposed change**: Revise to read: "*The pharmacovigilance system master file should also contain copies of signed agreements for significant delegated* ***pharmacovigilance*** *activities, such as:* • *"pharmacovigilance service provision (QPPV, safety data entry, PSUR writing, electronic ICSR reporting, evaluation of safety data, etc.);* • *"delegation concerning the pharmacovigilance system master file."*
309 to 316		Comment The content of the PSMF should be fully in accordance with that specified within the finalised implementing regulation i.e. there should be no additional requirements over and above that specified in the regulation. For example, noting that the current draft implementing regulation (articles 3 & 4) does not contain a requirement for a 'current list of studies' in the PSMF, this should <u>not</u> be specified within the GVP module and the requirement currently proposed in line 309 – 316 should be deleted.
313 to 315		Comment: The list of the studies is required "per active substance" which is not applicable to vaccines considering that a vaccine may include several substances e.g. a Pentavalent vaccine.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: Add text in italic "It should distinguish between interventional and non-interventional studies and should be organised per active substance *or antigen*".
375 to 376		Comment Current text is not clear what is meant by 'latest figures' . Recommendation: Amend text to say: an overview of the timeliness of PSUR reporting to competent authorities in EU ***over the past year***
377 to 379		Comment: This requirement lacks a timeframe Recommendation: Amend text to say: an overview of the timeliness of safety variations compared to deadlines submitted ***over the past year*** as well as the date and description of required safety variations that have been identified but not yet been submitted.
398-399		Comment: As in smaller companies in particular one individual may have more than one role it is suggested that resource management may also be captured as full time equivalents (FTEs). The information should be limited to staff employed by PV function. Recommendation: The organisational chart giving number of people ***or FTEs involved in activities within the pharmacovigilance function***
405-407		Comment Where possible, overlap with Module I –Pharmacovigilance systems and their quality systems, should be

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		avoided or be consistent. As Module I sets quality systems expectations whereas Module II sets required content, overlap should be avoided e.g. Training requirements are covered in Module I, I.B.7, line 193 -197. Recommendation: Remove requirement
443-447		Comment: The need to indicate within the product list what type of product specific safety monitoring requirements exist eg risk minimization measures, non-standard PSUR periodicity may present a practical problem. As the list is likely to be generated from a controlled system it is very unlikely that this additional information is available from the source system. Addition of these incremental requirements to the list would therefore be a manual process that would be highly impractical. It is therefore proposed that the Annex to the PSMF may contain additional lists that are more easily maintained eg a list of products with RMPs, list of products with specific safety monitoring requirements (adverse events of interest). We believe that the PSMF should describe the PV system but not include product specific outputs of the system therefore cross-reference or links to the product specific information should be sufficient.
453-463		
470		Comment: In addition, as the nature of the information provided by the sources described in II.B.4.8 is such that it can change frequently, maintaining a continuously updated version of the information in the PSMF is duplicative. Pulling such a breadth of detailed and constantly changing information from a multitude of sources into the PSMF also introduces significant potential for disconnect. It is therefore proposed that regular reports from respective systems are maintained in the PSMF for QPPV and MAH oversight purposes, but that up-to-date ad hoc reports are provided from the controlled system in the event of a 7 day/immediate request from a regulatory authority.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Recommendation Add additional text: ***Where content of PSMF Annex changes frequently e.g. product list, it is acceptable to maintain regular reports from respective systems for QPPV and MAH oversight however up-to-date ad hoc reports should be provided from the controlled system in the event of a 7 day/immediate request from a competent authority.***
472		Comment: As the PSMF is not routinely submitted to competent authorities there is no mechanism for them to be aware of changes other than QPPV details or location of PSMF. It is unclear therefore what could be the trigger for them to solicit information which could lead to MAHs receiving multiple ad hoc requests.
483-491		Comment: For those components of the PSMF that derive information from company controlled systems that are validated and have an associated audit trail, the source of the history of change should also be derived from the controlled system and not be duplicated in the PSMF. Recommendation: Insert new sentence after first sentence – ***Where the list content is derived from a controlled system then the history of change may also be derived from the controlled system.***
496-497		Extensive, significant or important descriptive changes to the content of the master file may necessitate a new version of the pharmacovigilance system master file to be produced, and these should be recorded in the logbook… Clarity is needed on what constitutes extensive, significant or important descriptive changes to go into

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		logbook, as opposed to what can be tracked in history of changes (line #490/491, described as product and SOP lists of compliance figures…)
515-519		Comment: Due to the nature of information contained in the PSMF, requiring the content and lists to be kept up to date continuously places an onerous administrative burden on industry. We would recommend that the PSMF should be updated periodically, at a minimum quarterly, and the most up to date version of the PSMF provided upon request. Recommendation: Amend text to say: 'The information shall be succinct, accurate and reflect the current system in place, which means that whatever format is used, it must be possible to keep the information **periodically updated** and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements'
583-584		Comment: it s unclear from the Guideline which Member State would be the supervisory authority for a centrally authorised product where a pharmacovigilance system is shared by several marketing authorisation holder as described in lines 191-203. Proposed change (if any): Please clarify further in the Guideline

Please add more rows if needed.

17 April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

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*).*

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

1. General comments

Stakeholder number ***(To be completed by the Agency)***	General comment
	The EGA members of the pharmacovigilance and regulatory working group support the change from DDPS to PSMF but we think that there is too much detailed information for the PSMF, which will require a huge effort to be compliant by Jul 2012. Additional guidance of implementation is urgently requested. It is our opinion that the PSMF should provide a broad and general overview of the PhV system. This document should present the PhV system without increasing the workload of a company, which in our opinion will happen with the requirements contained in GVP Module II. In relation with the transition period it is specified that the PSMF will have to be in place either at the time of the date of the following renewal or by 2 July 2015 whichever is the earliest. This statement gives a real transitional period only for innovator compounds but for generic companies as the number of marketing authorisations granted is so high a renewal is due almost monthly. Because of this transitional period will be inexistent for these companies.
	If the rationale behind the creation of a PSMF is to provide an overview of the Pharmacovigilance System and be compliant with the requirements, a global template could be important to harmonise its structure so that the organisation of the files be similar between the MAHs and could be easily assessed/audit/inspected by an external entity.

Stakeholder number *(To be completed by the Agency)*	General comment
	The information provided in the PSMF should continuously be updated. Further clarification should be provided regarding the timelines for updating the information and the deadline for each of the possible changes, if it is forecasted to have different deadlines according the modifications. The info concerning the contact details for the QPPV should not be included in the PSMF. Access should be foreseen for the QPPV to the EVMPD as the information will be there available and up-to-date. Reference to the most current update on the QPPV contact details can be made in the PSMF.
	PSMF is required for any new MA application after 02 July for centrally approved procedures and 21 July for all other routes of authorisation and for all renewals due after these dates. It is difficult to maintain both a PSMF and a DDPS in parallel and it useful to find a way how to move to PSMF for all products simultaneously. The transfer from DDPS to PSMF should not be seen as a variation, since this is a legal obligation to make this change and no fee should be charged for it.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 114-117		Comment: Retaining the need for a variation if changes to the summary of the PV system are difficult and Time/money consuming on the Industry and also for Regulators. As this location of the PSMF and the name and contact details of the QPPV are required to be submitted to EVMPD in accordance with Article 57 it is suggested that individual product variations should not be necessary and this requirement be removed.
Lines 126-132; also lines 245-6; also lines 567-73		Comment: If it is mandatory to have the location of the PSMF in the EVMPD and to keep this information updated by notifying the EMA, why is it also necessary to submit a variation if the PSMF location changes. This is an additional burden both for the NCAs and the MAH as the same information has to be submitted twice. The same comment applies to the QPPV contact details which are required to be provided to the EVMPD and within the PSMF Proposed change (if any): Single submission of updates to PSMF location and QPPV contact details as an update to the EVMPD by the MAH
Lines 143-147		Comment: If the MAH does not have any planned MA applications for submission soon after July 2012, then the first time they might introduce the PSMF could be by variation or renewal for an existing product. It is not clear how they will get the PSMF reference number in this case – will they have to register the PSMF in EVMPD before the variation/renewal is submitted, or will the reference number be provided once the variation/renewal is approved? Proposed change: explain how MAH should obtain PSMF reference number if they first introduce the PSMF as a variation/renewal for an existing 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')***
Line 148		Only info related to location of the PVSMF need to be submitted as a variation? Does this apply also for national CA?
Lines 168-174		Comment: There is a broad and subjective range of situations that could be included in these topics. The only two situations in which the notification to the QPPV needs to be documented are the ones described in lines 172-174?
Lines 172-174		Comment: If the QPPV signs the PSMF the acceptance in writing would be sufficient. Instead of particularly define which topics should be accepted by the QPPV, it should be mentioned that he/she should sign the document. Proposed change (if any): Inclusion of the topics in lines 173 and 174 as topics of the line 162 as well. Add the sentence: The QPPV should accept changes in the PSMF by signing it.
Lines 186-187		Comment: Please confirm that in the case of different MAHs sharing the same PSMF they must have the same QPPV. Proposed change (if any): Amending for readability: In either case, a single and specific pharmacovigilance system master file shall be in place to describe each system and a single QPPV should be responsible for that system.
Lines 220-227		Describes delegation of activities regarding the PSMF – it is assumed (but not explicitly stated) that this means delegation to a third party outside the MAH (rather than delegation within the MAH) since detailed written agreements are required to describe the delegation. It would be helpful if this was stated more clearly

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To 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 283-286		Please clarify "description of the delegated activities and/or services…" Is it supposed to detail the activities delegated as well as the procedure applicable? Is it acceptable to present this information in the form of a list of tasks delegated?
Lines 287-296		Comment: "links with other organization such as co –marketing agreements and contracting of PV activities…" Proposed change: The proposed list/table to show and identified all parties involved in PhV agreements is too detailed; we propose a broader description just describing the location and the nature of the contracts and agreements. The detailed information shall be made available in an inspection or upon request. Additionally, the local national agreements related to safety that are applicable only in one country should be provided to the competent authority of the country concerned should they request the PSMF. Lines 289 to 291 should be deleted, as follows: "(…) A description of the location and nature of contracts and agreements relating to the fulfilment of pharmacovigilance obligations should be provided. ~~This may be in the form of a list/table to show the parties involved, the roles undertaken and the concerned product(s) and territories.~~ This section may be organised according to; service providers (e.g. medical information, (…)"
Lines 297-298		Comment: copies of signed agreements for significant delegated activities (PV processes) applying to local contracted activities could mean many contracts in local language. We suggest that both signed global and local agreements for contracted activities be available upon request or during an inspection and not attached to the PSMF. Proposed change: "The Pharmacovigilance system master file should also contain general information on signed agreements for significant delegated activities, such as:'… After line 301 add: Copies of signed global and local agreements in a given country should be made available to the competent authority of the concerned country, should they request 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')***
Lines 297-301		Comment: What is considered a "significant delegated activity"? The topics referred to a broad range of activities. It seems that all licensing agreements have to be appended to the PSMF. Proposed change (if any): (see above) Copies of the signed agreements shall be made available in an inspection or upon request.
Line 308		Comment: The detailed information on contracts shall be made available in an inspection or upon request. Agreements can be listed or indicated in the PSMF, but not as detailed information.
Lines 309 - 316		Comment The size and nature of these lists of studies mean that there could be multiple changes occurring on a daily basis making continuous update of the PSMF practically impossible. This requirement therefore seems to be contrary to the stated objectives of the revised PV legislation – those of simplification and reduction of duplication and administrative burden. Recommendation: The PSMF should have links to the controlled systems for up-to-date information and a regular e.g. monthly report is generated and retained in the PSMF for QPPV oversight.
Lines 317-319		Comment: If flow diagrams are represented to describe the process for ICSRs, there is no need to provide a detailed description of the process, as it is described in the company's SOPs. Proposed change (if any): Delete lines 318-19.
Lines 326-332		Comment: There are procedures in place to manage databases and computerised systems and therefore, we

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***
		think there is no need to detail the procedures for the management of those systems, such as system functionalities, testing and back-up procedures. If need, the MAH shall provide all the documentation related to the computerised systems and databases. The PSMF shall include the main PhV activities covered by the databases, the validation status of the system and the nature of documents related to the systems. This should be similar to what is described already in the DDPS.
Line 337		Comment: Please further clarify the meaning of "the nature of the data held" (is it information what information is collected from a case e.g. the adverse reaction term?)
Line 340		Comment: Please clarify "a description of the process, data handling and records …" Replace by "A list of the procedures related to PhV activities", as it is a huge workload to provide a detailed information on SOPs, as they are accessible and make available upon request. This section should be simplified to a list of procedures related to PhV activities.
Lines 378 - 380		Comment: This requirement lacks a timeframe Recommendation: Amend text to say: an overview of the timeliness of safety variations compared to deadlines submitted ***over the past year*** as well as the list with date and description of required safety variations that have been identified but not yet been submitted.
Line 395		SOPs belonging to service providers and other third parties should be clearly identified". We Suggest mentioning, in the requested list, only SOPs related to Global contracted activities. Specific country Third party SOPs should not be listed unless PVSMF submission is to national competent authority. Proposed change: SOPs of third parties and service providers belong to Third parties and they are responsible for maintaining them. There is no need to have the SOPs since the tasks are defined in the PhV agreements and contracts.

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To 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 397-403		Proposed change (if any): Replace lines 399 to 403 by: ▪ the organisational chart giving the approximate number of people involved in pharmacovigilance activities, including a reference to the location of their qualification and training records (centrally or locally); ▪ a listing of sites where the personnel are located.
Line 398		This line refers to 'resource management' but the subsequent bullet points make it clear that what is required is a simple org chart with numbers of PV staff available at each site. Resource management implies a lot more than a count of the number of staff; suggest this simply refers to 'resources'
Lines 398-399		Comment: As in smaller companies in particular one individual may have more than one role it is suggested that resource management may also be captured as full time equivalents (FTEs). The information should be limited to staff employed by PV function. Recommendation: The organisational chart giving number of people *or FTEs involved in activities within the pharmacovigilance function*
Lines 390-396		Comment: The processes (standard operating procedures) are also described in section II.B.4.5 and the assessment of the procedures in section II.B.4.6. In order to avoid duplication of information can the information be cross referenced between sections?
Line 400		Comment: Please clarify the request for reference to location of qualification records in the organisational chart.

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To 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 404		Comment: Please clarify "instructions on critical processes". What sorts of things are envisaged to be critical processes, and what information needs to be included here??
Line 411-2		A "current list of scheduled and completed audits concerning PV system" is required. There is no information here on how far back this list should go with regard to previous audit dates. It might be assumed that this should be the number of years as indicated in section II.B.4.8 (line 463) but it would be helpful to identify the timeline here.
Lines 417-426		Comment: The EGA considers that there is no need to provide too detailed information. It should be sufficient to provide the audit dates and scopes, along with major and critical findings. In any case, all this data are described in particular documents (audit plan, audit reports, CAPA) without the need to duplicate data. These documents should be easily retrieved if requested, but a full summary should not be mandatory in the PSMF. Proposed change (if any): delete lines 417-426
Lines 420, 421, 422, 424		Proposed change (if any): replace "preventative" by "preventive".
Line 425		"Corrective action... has been independently verified". We suggest specifying what "independently" means. Proposed change: Add "The independent verification is to be performed by auditors or by an operational function which is independent from the auditee's line management. "
Lines 432-435		Comment: In a generic medicines company with thousands licenses "a list of medicinal products" is outdated the moment it is printed. Therefore to have this continuously annexed to a document makes no sense, since it would require the log to be updated with every change in license/contract. In any case, all licenses in the EU of a MAH are available in the EudraVigilance database as of July 2012, following art 57(2), so there is no need for separate provision.

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***
		The MA conditions are known by the authorities and therefore, for thousands licenses it will become a nightmare to have an updated list of medicinal products with details on product specific safety monitoring requirements, among other details.
Line 442		The product list should include "presence on the market" – clarity on what this means would be helpful. For instance, if a product has been launched onto the market but then is temporarily unavailable because of an interruption to supply, would we need to update the product list to indicate that the product was not currently present on the market, and then update again when supply resumed. Or would we just mark a product as no longer marketed when supply/sales stop and there is no intention to market again?
Line 443-447		The need to indicate within the product list what type of product specific safety monitoring requirements exist e.g. risk minimization measures, non-standard PSUR periodicity may present a practical problem. As the list is likely to be generated from a controlled system it is very unlikely that this additional information is available from the source system. Addition of these incremental requirements to the list would therefore be a manual process that would be highly impractical. It is therefore proposed that the Annex to the PSMF may contain additional lists that are more easily maintained e.g. a list of products with RMPs, list of products with specific safety monitoring requirements (adverse events of interest). We believe that the PSMF should describe the PV system but not include product specific outputs of the system therefore cross-reference or links to the product specific information should be sufficient.
Lines 449-452		Comment: A marketing authorization can be included in more than one PSMF. Further details should be provided to explain this possibility
Line 463		"list of scheduled & completed audits…" for completed audits the cut off is "for a period of ten years" which is too much information for large companies.

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***
		Proposal: 2 years
Line 470		Recommendation Add additional text: *Where content of PSMF Annex changes frequently e.g. product list, it is acceptable to maintain regular reports from respective systems for QPPV and MAH oversight however up-to-date ad hoc reports should be provided from the controlled system in the event of a 7 day/immediate request from a competent authority.*
Line 472		Comment: As the PSMF is not routinely submitted to CAs there is no mechanism for them to be aware of changes other than QPPV details or location of PSMF. Recommendation Amend text to say: *MAHs may notify CAs* about important changes to the PV system
Lines 483-491		Comment: For those components of the PSMF that derive information from company controlled systems that are validated and have an associated audit trail, the source of the history of change should also be derived from the controlled system and not be duplicated in the PSMF. Recommendation: Insert new sentence after first sentence – *Where the list content is derived from a controlled system then the history of change may also be derived from the controlled system.*
Lines 490-492		Would updating of the list of open audit findings be managed by change control or would the removal of an audit finding where the CAPA had been closed always require an update to the log book. Sometimes the CAPA may have a knock on effect to the main PSMF content, in which case the log book would obviously need

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		updating, but in other cases the CAPA might not require a change to the PSMF other than to remove the finding from the document.
Line 490-500		Please clarify the meaning of "extensive, significant or important descriptive changes to the content of the PSMF".
Lines 612-13		Mentions making public the contact information for PV enquiries- what information will be provided? For instance, a general mailbox/MI phone number – or is it planned to publish QPPV contact details? The former would be acceptable; the latter would not be acceptable for publication in the public domain.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18-April-2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Comment 1: According to Article 3 of Regulation EC 1235/2010, the requirement for the PV System Master File applies as follows; "to marketing authorisations granted before 2 July 2012 as from either; (a) the date on which those marketing authorisations are renewed or (b) the expiry of a period of three years starting from 2 July 2012". However, applications for new centralised marketing authorisations are subject to Article 8(3) ia of Directive 2001/83/EU as amended by 2010/84/EU which requires a reference to the location of the PV System Master File and Module II states that (line 111-2): "The requirement for the submission of a detailed description of the pharmacovigilance system with each marketing authorisation application is not (sic) longer applicable". The Module does not address the application in practice of the transitional arrangements.
	Recommendation regarding Comment 1: There needs to be clarification provided as to the relevance and application of the transitional arrangements in relation to the requirement to introduce the PV System Master File for those Marketing Authorisation Holders with centrally authorised products authorised prior to July 2 2012 and making applications for new marketing authorisations after that date.
	Comment 2: It is not practical to have "continuous" updating of the PV System Master File (line 516), and in particular, the annexes.
	Recommendation regarding Comment 2: Allow for the periodic updating of the PV System Master File at defined intervals proportionate to the scale and complexity of the Marketing Authorisation Holder's PV System, e.g. quarterly.
	Comment 3: Module II provides (line 235) that "essential documents" that describe the PV system shall be included in the PV System Master File. The references to the Implementing Measures in the Module do not match the revised draft Implementing Regulation.
	Recommendation regarding Comment 3:

Stakeholder number *(To be completed by the Agency)*	General comment
	Clarification should be added to Module II as to what comprises "essential documents" or the line should be deleted. References to the Implementing Regulation should be updated.

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 516		Comment: It is not practical to have "continuous" updating of the PV System Master File (line 516), and in particular, the annexes. Proposed change (if any): Allow for the periodic updating of the PV System Master File at defined intervals proportionate to the scale and complexity of the Marketing Authorisation Holder's PV System, e.g. quarterly.
line 235		Comment: Module II provides (line 235) that "essential documents" that describe the PV system shall be included in the PV System Master File. Proposed change (if any): Clarification should be added to Module II as to what comprises "essential documents" or the line should be deleted.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	In this draft Guideline on good pharmacovigilance practices (GVP) Module II - Pharmacovigilance System Master File very often "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.
	The line-numbering is not the same comparing published document Module II under http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/landing/landing_page.jsp&mid=WC0b01ac05801b7e46 (here on page 2 line 36 + line 37) with published document Module II sent before (here on page 2 line 36). It could be a deviation of 1 line.
	The PSMF is a very comprehensive document differing considerably from the previous DDPS and is applicable from July 2012. The Guidance document however will be available only shortly before this date. According to the transitional provision it could be the case that after receiving a renewal for a MA a MAH has to have in place the PSMF immediately after July 2012. Or a company might wish to submit an application for a MA shortly after July 2012. Therefore, an additional transitional arrangement should be established to allow the preparation of a correct and complete PSMF.
	The creation and in particular the maintenance of the new PSMF will be a new workload which is very challenging for smaller and medium sized companies with a smaller amount of case reports. The extent of updating should be reduced, e.g. II.B.4.8. (different appendices), II.B.4.3. (list of studies). The switch from the DDPS to the PSMF should be possible for all products of one MAH at the same time, e.g. via a grouped variation. It would be a duplication of efforts to have to maintain both a DDPS and a PSMF until all necessary variations for all individual products have been filed and approved.
	In the Question and answers document 163570 it is foreseen for already submitted applications, that applicants contact the

Stakeholder number *(To be completed by the Agency)*	General comment
	competent authorities, which may agree "on a case-by-case basis". This is an extensive workload and not feasible. Proposal: if a MAH has a PSMF in place, the MAH should inform all EU-authorities and the DDPS is not valid any more.
	The structure and organization of companies might differ considerably and as a consequence the PSMFs will also differ substantially. Therefore, a common template for the PSMF seems not to be appropriate.
	All abbreviations should be explained in the text (e.g. there is no explanation for "IM"). Furthermore, all citations should be checked (e.g. line 50 [IM Art 3(1)]) – citation does not fit to the corresponding 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')*
Lines 47-49 & 121-124		**Reference:** Section II.A. Introduction "The pharmacovigilance system master file shall be located either at the site in the EU where the main PV activities or the MAH are performed or at the site where the QP operates." **Comment:** If the PSMF is in electronic format, maintained in an electronic medium, the QPPV has access does the aforementioned statement require the availability of a hard copy on site if the server is outside the EU? **Proposed change (if any):** An electronic format should be sufficient irrespective of the location of the server as long as the PSMF can be made available within the timelines foreseen per Directive 2001/83/EC and Regulation (EC) No 726/2004.
Lines 68-69 & 121-124		**Reference:** Section II.B. Structure and Process "…the PSMF location, must be within the EU." **Comment:** If the PSMF is maintained in an electronic format does this mean that the server in which the document resides must be in the EU? If yes, does a hybrid system in which the PSMF is maintained electronically but available in hard copy at the location of the QP in the EU satisfy this 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')*
		Proposed change (if any): An electronic format should be sufficient irrespective of the location of the server as long as the PSMF can be made available within the timelines foreseen per Directive 2001/83/EC and Regulation (EC) No 726/2004.
Line 100 - 119		**Comment**: It should be clarified that this refers to the EU-QPPV (and not to local QPPVs, e.g. Stufenplanbeauftragte in Germany, if they are not EU-QPPV and do not have an oversight on the data outside of Germany).
Line 107 - 108		**Comment**: The statement signed by the applicant should be signed by both, the applicant **and** the QPPV. It is essential that the QPPV confirms to have the necessary means to fulfill the tasks and responsibilities. It is not clear what "Title IX" is and thus clarification is needed.
Line 113-116		**Comment**: "amendments…shall be submitted via a variation application…" **Proposed change (if any):** "amendments…shall be submitted in accordance…" [without variation]

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 140 - 141		**Comment**: "Once the database ….is functional…" – what will be required in the time before this status is achieved?
Lines 159-160		**Reference:** Since a specific QPPV has responsibility for the pharmacovigilance system, changes to the pharmacovigilance system master file should also be notified to the QPPV in order to support their authority to make improvements to the system. **Comment:** GVP module I – Pharmacovigilance systems and their quality systems mentions in section I.C.1.1. mentions that "The marketing authorisation holder should therefore ensure that the QPPV has access to the pharmacovigilance system master file (PSMF) as well as authority over it and is notified of any changes to it." **Proposed change (if any):** Change wording referenced above to: "Since a specific QPPV has responsibility for the pharmacovigilance system, **the QPPV has access to the pharmacovigilance system master file (PSMF) as well as authority over it and** changes to the pharmacovigilance system master file should also be notified to the QPPV in order to support their authority to make improvements to the system."
Lines 165 - 167		**Reference:** The types of changes that should be routinely and promptly notified to the QPPV are: • the addition of corrective and/or preventative actions to the pharmacovigilance system master file (e.g. following audits **and inspections**) and managed deviations from the processes defined 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')*
		quality management system for pharmacovigilance; **Comment:** There is no legal requirement to add corrective and/or preventative actions resulting from inspections to the pharmacovigilance system master file. This goes far beyond the requirements of the Directive, art. 104 (2). This kind of information should be available to both the QPPV and EMA/ the national competent authorities anyway and changes and to the PV system following inspection will also be reflected in the PSMF. **Proposed change (if any):** Remove **'and inspections'** from the sentence to read: "the addition of corrective and/or preventative actions to the pharmacovigilance system master file (e.g. following audits) and managed deviations from the processes defined in the quality management system for pharmacovigilance;"
Line 173		**Comment:** The QPPV should also be informed if she/he is no longer responsible for a product. Line 173 should be changed in *"inclusion of products into or deletion of products from the pharmacovigilance system for which the QPPV is responsible;"*
Line 189 - 191		**Comment:** How should "a QPPV" be understood? As one single person like in line 546? If yes, this should be clearly stated here.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		The headline of this section is "the representation of the pharmacovigilance system". The information given in line 189 – 191 however does not fit to this section and should therefore be included elsewhere.
Line 244 - 256		**Comment**: Directive states in Art.104(4) that "national competent authorities **may** request the nomination of a contact person for PV issues at national level" . But the guideline now states in II.B.4.1, that the PSMF **shall** include information relating to the contact person for PV where such a person has been nominated at national level. So this is more than originally requested in the Directive. **Proposed change (if any):** "shall" should be replaced by "may"
Lines 261-263		The details provided in relation to the QPPV should also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance (including registration with Eudravigilance). **Comment :** GVP module I – Pharmacovigilance systems and their quality systems mentions in section I.C.1.2. That "If the QPPV has not completed basic medical training in accordance with Article 24 of Directive 2005/36/EC, access to a medically trained person (i.e. in accordance with Article 24 of Directive 2005/36/EC) shall be available [IM Art 13(1)] and this access should be documented in the pharmacovigilance system 518 master file (PSMF) (see Module II)." **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')*
		This sentence from GVP module I – Pharmacovigilance systems and their quality systems mentions in section I.C.1.2. should also be mentioned in GVP module II - Pharmacovigilance system master file, section II.B.4.1. subsequent to the sentence in lines 261-263.
Line 267 - 318		**Comment**: Huge number of documents which are now to be included in the PSMF, and which have to be updated frequently (also local documents). Please also see general comment above (high workload, not feasible for smaller and bigger companies).
Line 286		**Comment**: "Links with other organisations… should be outlined." – How should this be in practice? The links are changing frequently. **Proposed change (if any):** "Information about links with other organisations … should be available on request"
Lines 291 – 292		**Reference:** " …service providers (e.g. medical information, auditors, patient support programme providers, study data management etc.), …" **Comment:** The activities performed by the example service providers given in the brackets are not pharmacovigilance obligations, hence inappropriate

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Replace examples by service providers performing e.g. case management, expedited reporting, aggregate report preparation, signal detection etc.
Line 296 - 297		**Comment**: The PSMF should contain copies of signed agreements for significant delegated activities. Such agreement might be voluminous documents and therefore expand the PSMF considerably. For the reason of transparency a list of agreements including the topics covered should be sufficient instead of complete signed agreements. **Proposed change (if any):** "Signed agreements for significant…should be available on request."
Line 308-315		**Comment**: "…current list of studies" – not feasible in practice, since they are changing frequently **Proposed change (if any):** "…current list of studies… should be available on request."
Line 334 - 338		**Comment:** The item "the nature of the data held (e.g. the type of case data retained for ICSRs)" is not clearly defined. The nature of data retained depends on the nature of data received on a specific ICSR. It seems not appropriate to list all the potentially retained data in the PSMF.
Line 339 - 340		**Comment:** It is unclear how "a description of the processes" should be understood. If it is expected that full SOPs are to be included in this section this would not be acceptable. Furthermore, it must be considered that SOPs

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		normally are written in the local language. A translation of all documents would be not feasible, especially for smaller companies.
Line 362 - 364		**Comment:** In line 363 "a table listing all pharmacovigilance related procedural documents" is required. This list seems to be appropriate to demonstrate that **all** applicable processes are addressed adequately by SOPs. We propose to present this list in the Annex of the PSMF.
Line 366 - 385		**Comment**: It is not clear which metrics are expected by the authorities (e. g. timelines) And shouldn't this be the duty of authority inspections, to evaluate the compliance with legal requirements?
Line 387 - 428		**Comments**: Requirements ("all major or critical findings, and the CAPA-Plan, and a reference to the full audit report"…) exceed the content of the EU-Directive, see Art.104(2): "He shall place a note concerning the main findings of the audit on the PSMF". **Proposed change (if any):** The obligatory requirements should be adapted to the EU-Directive (Art. 104(2)). **Comment:** In this section a list of documented procedures and processes including number, title and effective date is required. How is this list distinguished from the list required in line 363? Clarification is needed.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 403		**Comment:** According to Module I line 302 the wording should be changed in "instruction on critical **pharmacovigilance** processes".
Line 426 - 428		**Comment:** The item "quality management system" is not defined. If this should be a reference to module I "pharmacovigilance systems and their quality systems" than the item "quality system" should be used.
Line 417 - 419		**Comment:** From our point of view it is sufficient to include critical findings from the audits into the PSMF. Therefore, "major or" should be deleted.
Line 431 - 434		**Comment 1:** (1) In case only one PSMF exists in the company an annex which lists all medicinal products is redundant as this information is contained in the EVMPD which contains details about the location of the PSMF (line 126) / "A list of medicinal products" – not feasible and already provided. **Proposed change (if any):** "A list of substances is mandatory. A list of medicinal products … should be available on request" **Comment 2:** The list of substances should include the INN of the active substance. However, for herbal or homoeopathic active ingredients no INN exists. How should these substances be named? In the same way as on the label? The naming of the substances should be consistent with the information to be transmitted to EMA according to Art 57 (2) of the regulation (EC) No. 726/2004.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 3: Requirements ("shall contain…a list of all completed audits for a period of 10 years"…) exceed the content of EU-Directive **Proposed change (if any):** The obligatory requirements should be adapted to the EU-Directive.
Line 463 - 465		**Comment**: It is not clear what "performance indicators" are? This is redundant to line 383 (targets for the performance of the PV) and line 373 (metrics to monitor the quality)
Line 471 - 511		**Comment**: Consequently to comments in II.B.4.7 (line 387 – 428) and II.B.4.8 (line 430 – 470): process/activities to implement change control systems to this extent are not feasible for small and middle sized companies
Line 483-488		**Comment**: see comment concerning 431-434

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 489-499		**Comment:** How to document the history of changes and the logbook in a feasible way? Is it really mandatory to describe any changes? **Proposed change (if any):** All versions should be archived. There is no need to document all changes in detail.
Lines 517		**Reference:** "… it must be possible to keep the information **continuously** up to date …" **Comment:** 'continuously' has been deleted from the current draft of the Implementing Regulation, hence is should be removed here. **Proposed changes (if any):** The sentence should read: " ...it must be possible to keep the information up to date…"
Lines 530 - 538		**Reference:** The pharmacovigilance system master file should be written in English (unless the marketing authorization holder only holds approvals in one Member State when it can be written in the EU official language for that territory), indexed in a manner consistent with the headings described in the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC [IM Art 4] and this guidance and allow easy navigation to the contents.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: The headings in the Concept Paper on the IM and in this module do not match and appear in different order, the final version of the IM is not yet available. Hence it is not quite clear how the PSMF should be indexed. **Proposed changes (if any):** It should be ensured that the headings in the final versions of the IM and this GVP module are consistent, otherwise the "**and**" in "...indexed in a manner consistent with the headings described in the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC [IM Art 4] and this guidance …" should be replaced by "**or**".
Line 540 ff		**Comment:** The information in this section is only a repetition of information given in the sections above. Therefore II.C.1.1 could be deleted completely.
Line 560 - 565		**Comment**: In case section II.C.1.1 will not be deleted completely (see comment above): The information in the two sentences of this paragraph seem to be redundant.
Line 633 - 636		**Comment:** Concerns have been raised by contract QPPVs who perform work from their homes regarding the publication of the location of the PSMF via a publicly available website.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18/04/12

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
Faculty of Pharmaceutical Medicine

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

1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
50		Comment: This line and various others refer to the Implementing Measures. It is confusing to have two documents to describe the same processes. Proposed change (if any): Incorporate all relevant information from the Implementing Measures into this and other GVP guidelines, as applicable.
53 - 54		Comment: This section states that there is no requirement for variations for changes in the content of the PSMF, yet lines 114 to 117 state that amendments to the particulars or documents referred to in the PSMF shall be submitted via a variation. Proposed change (if any): Please could these seemingly contradictory statements be clarified.
Page 3 line 68		Comment: Need a possessive ‘s after (QPPV) Proposed change (if any): Add ‘s
Page 4 – line 113		Comment: Change “not longer applicable” to “no longer applicable” Proposed change (if any): change not to no
121 - 139		Comment: Since there are instructions regarding the location of the PSMF, does this mean that if kept electronically, the server where the file is held electronically must be located within the EU? Proposed change (if any): It would be helpful if the issue of location was clarified as this has caused some considerable discussion / confusion.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 7 – line 228		Comment:– add "it" before "is advised Proposed change (if any): as above
Page 8 – line 250		Comment:– this should be a bullet point Proposed change (if any): make this sentence a bullet point
Page 8 – line 255		Comment: can the Agency provide a list of countries in the EU where it is required to have a local qualified person? Proposed change (if any): EMA to provide a comprehensive list of EU countries where it is a legal requirement to have a local qualified person for PV
Page 9 – line 297		Comment: it is not practical or value added to include actual copies of signed agreements within the Master File – a list detailing where agreements are in place should be provided and the actual agreements available on request Proposed change (if any): remove the need to include signed copies of the contracts in the PMF
Page 11 – line 376		Comment: "to" missing Proposed change (if any): insert "to" before "competent authorities
384		Comment: This section refers to the Annex of the PSMF. Proposed change (if any): Since this is the first time the Annex has been mentioned a cross reference to section II.B.4.8 should be made.
417 - 426		Comment: Once post-audit CAPA have been implemented, the note regarding audit findings can be removed from 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')*
		Proposed change (if any): Clarification is required as to what is required in the file regarding the audit, after this note is removed.
Page 12 – line 443		Comment: how similar do the products in the non-EU countries have to be to the EU authorised products to be included in the Annex? Proposed change (if any): - clarification requested
Page 14 – paragraph starting at line 514		Comment:– do we have 7 days or can immediate access to the PMF be requested Proposed change (if any): – please clarify as this is confusing

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
Gilead Sciences International Limited

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Throughout the document reference is made to extensive annexes of supporting information for the PVSMF that will be utilised for inspection purposes. In many instances changes can be very frequent and maintenance in a current state burdensome. Collating data for a periodic update of the PVSMF seems more appropriate, but would also require inspectorate acceptance of this approach.
	The format of the PVSMF is likely to be electronic, and with multiple annexes, very large. While provision of the full PVSMF within 7 **working days** may be reasonable, the expectation for the PVSMF and all annexes immediately upon request is not and should be limited to the main body.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
227 & 448		Comment: The text regarding shared PVSMFs is hard to follow as to what is required. Current practice with the DDPS enables product specific addenda – is such an approach feasible with the PVSMF?
292		Comment: Please clarify study data management providers being required for the PVSMF – is this only where PV services are provided e.g collection and/or submission of safety reports – the expectation is unclear.
315-316		Comment: Continually generating an up to date list of clinical trials has a high impact on resource.
321		Comment: Such data is documented in computer management change control SOPs and system change documents. What is the expectation of additional documentation in the master file?
322		Comment: What would constitute assessments of systems for fitness for purpose?
404		Comment: Resource management to include instructions on critical processes – what does this mean?
469		Comment: Requires maintenance of a log book, example headings would help together with guidance as to how this differs from 487 and up versioning of the PVSMF in 495 – generally changes would result in a new version?

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
H. Lundbeck A/S

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

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

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

1. 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')*
164,419-421, 423		Comment: Use of term ”preventative" and "preventive". Module II use term “preventative” however in Module I term “preventive” is used. Proposed change (if any): Please consider harmonising use of term ”preventative" and "preventive" within the Modules
403		Comment: Unclear how we should define critical processes Proposed change (if any): Please clarify the requirement.
417		Comment: Refers to significant findings - will summarizing of these per 419 be enough or is a listing also required? Proposed change (if any): Please clarify the requirement.
407-428		Comment: The requirement to include a note associated with any audit where significant findings are raised into PSMF might cause pressure to QA for reporting less major and critical findings. Proposed change (if any):
418		Comment: Reference to EU criteria for major and critical finding is missing from the text Proposed change (if any): Please add reference to EU criteria for major and critical finding

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
424-425		Comment: "Corrective and/or preventative actions have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or independently verified. Please clarify whether or not preventative actions also need to been demonstrated or independently verified for the note to be removed. Or if for the preventative part, demonstration of significant improvement is sufficient, without the requirement for full implementation of the preventative action, if applicable. Proposed change (if any): Please clarify the requirement.
462		Comment: "A list of all completed audits, for a period of ten years and a list of audit scheduled". Please clarify does this mean retrospective list of audits covering previous 10 years as well as audit schedules at the time of issuing initial version of the PSMF. Proposed change (if any): Please clarify the requirement
416-425		Comment: Re to comment related to Line number 462 if intention is to have information of audits available in PSMF retrospectively from last 10 years it might be challenging for the MAH to collect all information of the audits due to changes occurred during last 10 years (e.g. merges and acquisitions of companies) in addition full information of implementation of corrective and preventive actions might not be available for all audits due to company's procedure to close internal audits and follow up on external audits. Proposed change (if any): Please consider the period of audits to be included in the PSMF at the time of implementing the PSMF.
583-584, 191-203		Comment: Re to Lines 583-584, it s unclear from the Guideline which Member State would be the supervisory authority for a centrally authorised product where a pharmacovigilance system is shared by several marketing authorisation holder as described in lines 191-203.

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

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
National Authority of Medicines and Health Products INFARMED, I.P. Portugal

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

1. General comments

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

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>
April 16th, 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	A lot of the information required in the PVSMF does not belong to the Pharmacovigilance department but are disseminated in numerous departments of the company. For example list of authorized products is produced and maintained by the regulatory affairs department most of the time with specific electronic tools; list of contracts are produced and maintained by the legal department with specific tool. It will take a real amount of time to find solutions to compile all this information in one single document and to find an appropriate process to keep this document up to date for all the different aspects. Transitional measure taking into account the date of the next renewal or next application should be applicable only to replace the DDPS with a summary in the dossier and to stop updating the DDPS with variations except for information contained in the summary (to be confirmed). The PSMF should be mandatory only in 2015 in order to all MAHs to have enough time to find an appropriate process to produce and update this document in a suitable way.

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 120		Comment: please specify where in the dossier the summary should be placed (replace the DDPS in module 1.8.1? Proposed change (if any):
Line 165		Comment: add the deletion of preventive/corrective actions when the actions are closed. Indeed the lines 420 to 426 indicate that the note can be removed when the action is implemented or verified. Proposed change (if any): the addition of corrective and/or preventive actions to the pharmacovigilance system master file (e.g. following audits and inspections) **or deletion of theses actions when closed** and managed deviations from the processes defined in the quality management system for pharmacovigilance
Line 165		Comment: add only the preventive/corrective actions that are considered as major or critical (as in the paragraph IIB4.7. "Auditing", line 419). Simple comments and minor deviations could not be included in the pharmacovigilance system master file. Proposed change (if any): the addition of **major or critical** corrective and/or preventive actions to the pharmacovigilance system master file (e.g. following audits and inspections) **or deletion of theses actions when closed** and managed deviations from the processes defined in the quality management system for pharmacovigilance

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

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

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	A major concern about the proposed content of the PSMF is the combination of a PV system descriptive component and a PV system performance component (including the annex to the PSMF) into one document. This will likely result in a PSMF document that is considerably larger than the current Detailed Description of Pharmacovigilance System (DDPS). In addition, the 2 components will differ in terms of their maintenance requirements, i.e. how often they will require to be updated. For example, the descriptive component will be relatively stable, similar to the current DDPS; however, the system performance component will require more frequent updating (e.g. monthly or quarterly). Further, the 2 components also differ with respect to the submission of a PSMF within 7 calendar days to fulfil a regulatory authority request. Although it is possible to meet the 7 calendar day timeline for submitting a stand-alone descriptive component, submission of the entire PSMF with an up-to-date system performance component will place a significant administrative burden on the MAH. Upon review of the requirements of the PSMF content, a number of requirements for data and current status information are similar to those for the UK MHRA's System of Pharmacovigilance System (SPS). As per the "Guidance Notes on the Information Requested For an MHRA Statutory Pharmacovigilance Inspection", the MHRA "aims to allow companies at least 4 weeks to complete and return the SPS; in some cases the time frame may be shorter than this". The provision of up-to-date data, by the collation of up-to-date information from all the different data sources within an organisation, within a 7 day timeline is very challenging. The request for the PSMF by the competent authorities is referenced in a number of places within the Module. In addition, these references appear to be contradictory, and could therefore lead to differing interpretations between and among competent authorities and MAHs: *Line 78-81* *The pharmacovigilance system master file provides an overview of the pharmacovigilance system, which may be requested and assessed by national competent authorities during marketing authorisation application(s) or post-authorisation.* *Line 552-553* *During the evaluation of a marketing authorisation application the applicant may be requested to provide a copy of the pharmacovigilance system master file for review.* *Line 578-581*

Stakeholder number *(To be completed by the Agency)*	General comment
	The full pharmacovigilance system master file may be requested at any time, for example, to review the description of a pharmacovigilance system of an applicant that has not previously held a marketing authorisation in the EU or where specific concerns about the pharmacovigilance system and/or the product safety profile exist..... *Line 629-632* *The pharmacovigilance system master file should not routinely be requested during the assessment of new marketing authorisation applications (i.e. pre-authorisation), but may be requested on an ad hoc basis, particularly if a new pharmacovigilance system is being implemented, or if product specific safety concerns or issues with compliance with pharmacovigilance requirements have been identified.* Finally, it should be noted that some non-EEA countries have implemented PV requirements that are closely aligned to those of the EEA, as per current Volume 9A. As a result, this MAH has received requests for the company's global DDPS as part of the MA application assessment by a non-EEA country. In order to avoid the potential consequence of having to submit an entire PSMF to non-EEA countries who could decide to closely align to the new EU PV requirements, the need for additional clarity on the situations in which the entire PSMF will and will not be requested is especially warranted. Proposed change (if any): Therefore, it is recommended that the Module makes it explicitly clear that the submission of the entire PSMF *should be limited to "for cause" circumstances*. Further, as the PSMF shall be permanently available for inspection purposes (scheduled as well as unannounced), *that the regulatory authority considering making a request should also take into account the timing and outcome of the last inspection carried out by the supervisory authority, including the current status of any resulting corrective and preventive actions*. In addition, consideration should also be given to a 7-day request for the descriptive component of the PSMF *plus targeted request(s) for specific sections of the performance/ compliance component that will address the particular concern(s) of the competent authority*. Additional follow-up information can be requested and provided as required.
	The Annex to the PSMF should be that part [of the PMSF] that contains those components which will be subject to continual updating. This includes those components which provide current status of contractual agreements, and studies/registries/surveillance or support programmes, a list of documented procedures and processes related to pharmacovigilance activities, as well as compliance monitoring and system performance information. This will facilitate the ongoing maintenance of the descriptive PSMF sections referenced in Module section II.B.4.1- II.B.4.7. However, the Module as currently drafted appears to require information that will be subject to continual updates to be included in section II.B.4.1-II.B.4.7., when they would be more appropriately housed in the Annex to the PSMF. Proposed change (if any): This module should be revised to clearly indicate that all data which is subject to continuous updates

Stakeholder number *(To be completed by the Agency)*	General comment
	should be in the Annex to the PSMF and not part of the main descriptive component.
	The Module makes references to Commission Regulation (EC) No 1234/2008 and the associated Guideline (Variations regulation). This will require updating in order to ensure alignment with the requirements for variations to the particulars or documents referred to in the summary of the applicant's pharmacovigilance system.
	Additional transitional arrangements would be useful to explain how to move all products from the DDPS to the PSMF at one time.

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 92-96		Comment: This sentence appears suggest that the PSMF will be submitted for routine planning purposes in addition to 'for cause' situations (see general comment above regarding 'for cause' submissions). This would be particularly burdensome if all MAHs in the EEA are asked to submit a PSMF. Some MAHs may utilise the same PSMF and routine submission of this kind would result in duplicate submissions from multiple MAHs Proposed change (if any): Clarify the circumstance in which a request to all EEA MAHs may be required as above.
Line 94		Comment: It is not clear how detailed the history of changes is expected to be. For example, changes to procedural documents, minor version number upgrades to software systems, administrative changes, etc. can happen frequently. It should not be required that this level of change is documented. Proposed change (if any): It should e clarified in this section that only significant changes to the PSMF should be noted in the history of changes and that minor changes that do not materially impact the operation of the PV system should be excluded from this list.
Lines 127-132		Comment: It is not clear whether the notification of changes to the Agency also needs to happen via a variation as suggested for the national competent authorities Proposed change (if any): Add clarification on the mechanism to be used for such notifications to the Agency and the national 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 144		Comment: Will it be possible for a marketing authorisation to refer to more than one PSMF? For example, a particular product may utilise aspects of multiple PV systems, as in the case of products with both OTC and Rx licences. Additional clarity on how PSMF for dual-licence products should be constructed. Proposed change (if any): We suggest the marketing authorisation for such product should reference all applicable PSMFs.
Lines 159-174		Comment: It is not clear whether proof of the notifications to the QPPV listed in this section should also be included in the PSMF. Any changes impacting the PSMF notified to the QPPV would already be reflected in the history of changes document as the PSMF is updated. Proposed change (if any): Clearly state that proof of notifications may be held outside of the PSMF, but must e retained according to quality system requirements for record management.
Lines 164-166		Comment: It is not clear here the level of seriousness in the deviation or CAPAs should be notified to the QPPV and listed in the PSMF? Proposed change (if any): Suggest that it is consistent with lines 417-420 regarding only critical and major findings should be notified for addition to the PSMF.
Lines 205-207		Comment: It should also be noted that it is possible for a PV system to be utilised by a number of individual MAHs. Proposed change (if any): This scenario should also be addressed here.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 258-260		Comment: The list of tasks that have been delegated by the QPPV are not usually subject to continual change, and so should remain in the section (II.B.4.1.), and not in the Annex section. Proposed change (if any): A list of tasks that have been delegated by the QPPV shall also be included in the description of the PV system.
Lines 297-298		Comment: A list of agreements should be considered sufficient. As agreements are subject to continuous review and updating, the inclusion of copies of signed agreements will impose significant administrative burden for little apparent value. Specific copies of agreements may be provided upon request. Proposed change (if any): A statement should be added to clarify that the PSMF should contain a reference to the location of source data for such agreements where this is held in a validated system outside the PSMF.
Lines 309-316		Comment: The types of documents listed in this section are subject to frequent changes. This would require a continual change process to the PSMF. Can the regulatory body define a timeframe to update these types of lists within the PSMF (e.g. monthly, bimonthly, quarterly, and of course when submission is requested). Proposed change (if any): It should be sufficient to refer, for example, to the company's official data source/system where details of clinical trials, registries, etc, are being captured rather than pulling such data into the PSMF on a periodic basis. If included in the PSMF, it should be clearly stated that such data be contained within the Annex to the master file.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 366-386		Comment: For the section on PV system performance, this section should contain a description of the ongoing monitoring of performance of the system and the compliance of the main outputs of pharmacovigilance. However, due to the continual need for updates, actual outputs from the PV system demonstrating performance and compliance should be housed in the Annex. Proposed change (if any): 'A list of performance indicators and any outputs from the list above should be provided in the Annex…'
Lines 373-385		Comment: There should be more guidance here as to the time periods over which these parameters should be reflected in the PSMF as is provided in lines 371-372 (e.g. for the last year, or 2 years). Proposed change (if any): 'This should include information provided by competent authorities regarding the quality of ICSR reporting, PSURs or other submissions over the past year... an overview of the timeliness of PSUR reporting over the past year...and overview of the timeliness of safety variation submissions...over the past year'
Lines 413-416		Comment: It is not clear if the list of audits should also include marketing partner audits. Proposed change (if any): Add clarification on this point
Lines 416-426		Comment: For large companies, in particular, it should be sufficient to update audit findings in the PSMF on a periodic basis (e.g. monthly or quarterly). Activities required to update audit results continuously would result in a significant administrative burden as large companies may conduct quite frequent audits. Proposed change (if any): Add clarification that audit findings can be routinely updated in the PSMF on a periodic basis

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 458-461		Comment: The scope of "contractual agreements covering delegated activities" is not clear. Proposed change (if any): Please clarify whether the list of contractual agreements should also include licensing partners, distributors as stated earlier in lines 289 – 294.
Line 462		Comment: The Annex to the PSMF should specifically house current status/performance/compliance related information, and should not be descriptive. This allows the Annex to be continually updated, whilst allowing the description of the system to remain relatively stable. Proposed change (if any): The list of tasks delegated by the QPPF should be removed from this section and added to the descriptive component of the PSMF in order to maintain a clear distinction between the performance component, which will be continuously updated, and more stable elements to be included in the descriptive component of the PSMF (please see general comment on this)
Line 463		Comment: What is the rationale for selecting a period of 10 years for completed audits to be included? Such a list could be lengthy, especially for larger organisations, and may bear little or no relevance to the current status of a pharmacovigilance system. Proposed change (if any): Consideration should be given to a shorter duration and in relation to previous inspections of the PV system by the supervisory authority/national competent authority.
Line 473		Comment: As the PSMF is not routinely submitted to competent authorities there is no mechanism for them to be aware of changes other than QPPV details or location of PSMF. It is unclear therefore what could be the trigger for them to solicit information. Proposed change (if any): Amend text to say: 'MAHs may notify competent authorities about important changes to the pharmacovigilance system'

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 517		Comment: With the amount of data required in the PSMF and the number of sources from which it must be derived the possibility of real-time data is unrealistic. We, therefore, request the Agency to provide additional guidance on the meaning of *"continuously up to date"*. Proposed change (if any): A definition of "continuously up to date" should be provided
Lines 633-636		Comment: We question value of providing full transparency of the location of the master file via the Agency web-portal to the public.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Version date: 19 Jun 2012 10:13:00

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

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

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

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

Declaration:
The author is signing to confirm that this document has been prepared in accordance with Novartis standards for commenting and impact analyses of regulatory guidelines. The review team has assessed that the operational aspects of this guideline are scientifically appropriate and achievable by the Drug Safety 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
	We understand that as the document is electronic, the use of links to other documents which may not be located at the same site as the master file will be permitted e.g. links from the master file to SOPs held in a controlled system. Please clarify.

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')*
113-116		Comment: An abbreviated and dedicated notification procedure must be established to avoid great administrative burden and costs for MAHs and Health Authorities as in case of changes of the QPPV, contact details or PSMF location variations have to be filed for all EU/EEA marketing authorisations of a company. This notification procedure should not be part of the variation process but rather a stand alone procedure specific to this type of administrative changes. Proposed change (if any): Submission of a summary of the applicant's pharmacovigilance system to be just included in the marketing authorisation application. For registered products, it must be sufficient to notify the HAs about the new information via an abbreviated and dedicated notification valid for throughout EU/EEA for all marketing authorisations affected.
122-124		Comment: The module states that the master file should be located in the EU and that this is irrespective of content. If the file is electronic does this imply that the server where the file is stored should also be located in the EU or can it be located outside the EU provided that the physical office address of the master file is within the EU. Proposed change (if any): none

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
196-200		Comment: If the partner to whom the activity has been delegated is not active in EU/EEA, there may be no PSMF available. Proposed change (if any): Please clarify what action MAH should take in this circumstance.
257-259		Comment: Not clear if internal delegation (within the company, e.g. delegation of product-specific knowledge to the product safety expert) or delegation to other partners (e.g. license partner) is meant. Proposed change (if any): Please clarify
278, 279		Comment: The definition of what is in scope for study data management sites is required as this is very broad from any contract data management tasks to external collaborative partners, with a very broad range of activities. Proposed change (if any): Please clarify
308		Comment: Maintenance of listings should be on a regular basis (quarterly). Due to great and fast changing content of the requested lists, the list is not accurate any more once printed or generated. Therefore a list generated on e.g. a quarterly basis should be acceptable to get an overview for inspection preparation. Current listings can be provided to inspectors on request during the inspection. Proposed change (if any): Please clarify if quarterly updates are acceptable
320-322		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')*
		More details on the scope regarding databases are needed. Scope should be reduced to “main databases”. Proposed change (if any): A listing of the main databases used to receive, collate record and report safety information and an assessment …. Shall be described in the PSMF.
377-379		Comment: More details about the scope of a safety variation are required. Proposal: variation covering all (medial) safety issues (i.e. excluding quality related, e.g. shortage of shelf-life due to OOS results). Proposed change (if any): For example: Safety variations are variations that refer to safety issues, requiring a change of the Summary of Product Characteristics (SmPC), Package Leaflet (PL) and/or Labelling, which does not need to be implemented via an Urgent Safety Restriction (see below), but should be implemented as soon as possible.
382-385		Comment: A list with performance indicators to be provided in the annex is described in both bullet points. Proposed change (if any): Delete last bullet point.
394-395		Comment: The module states that the list of documented procedures should include those belonging to service providers and other third parties. Is the expectation that we give details of the SOPs used by all companies distributing our products? (DS) SOPs of service providers and partners are usually not available. Prequalification / audits ensure that the third party has PV appropriate processes in place.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Remove sentence
396-406		Comment: It is not clear what it is required for the description of resource management: e.g. • Number of people within safety function (global or local?) or within whole company • Number of people is changing frequently. A quarterly/monthly approach should be sufficient to reflect this topic. • Please clarify what is meant by training concept • Please clarify what is meant by qualification records (is this equivalent to training records or training files) • Please clarify what is meant by training files (is training material meant?) • Please clarify what is meant by instructions on critical processes (references to SOPs or working instructions?) Proposed change (if any): Please clarify as above
436-441		Comment: Data required here are already in the scope of the article 57(2) and will already be maintained centrally in the XEVMPD. In addition, data included in the XEVMPD should be subject to regular checks by Health Authorities so maintaining such a list within the annex of the PSMF seems redundant. Proposed change (if any): Novartis suggests deleting this 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')*
469-471		Comment: It is required that a logbook be kept of the changes made to the PSMF. As SOPs mentioned in the PSMF will be kept in controlled systems with version control and change history is it necessary to include details of the changes to the SOPs in the logbook or is it sufficient to simply note that the version of the SOP has changed. Proposed change (if any): Please clarify requirement

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
Procter & Gamble

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

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 3 line 68		Comment: Need a possessive 's after (QPPV) Proposed change (if any): Add 's
Page 4 – line 113		Comment: Change "not longer applicable" to "no longer applicable" Proposed change (if any): change not to no
Page 7 – line 228		Comment:– add "it" before "is advised Proposed change (if any): as above
Page 8 – line 250		Comment:– this should be a bullet point Proposed change (if any): make this sentence a bullet point
Page 8 – line 255		Comment: can the Agency provide a list of countries in the EU where it is required to have a local qualified person? Proposed change (if any): EMA to provide a comprehensive list of EU countries where it is a legal requirement to have a local qualified person for PV
Page 9 – line 297		Comment: it is not practical or value added to include actual copies of signed agreements within the Master File – a list detailing where agreements are in place should be provided and the actual agreements available on request Proposed change (if any): remove the need to include signed copies of the contracts in the PMF

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To 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 11 – line 376		Comment: "to" missing Proposed change (if any): insert "to" before "competent authorities
Page 12 – line 443		Comment: how similar do the products in the non-EU countries have to be to the EU authorised products to be included in the Annex? Proposed change (if any): - clarification requested
Page 14 – paragraph starting at line 514		Comment:– do we have 7 days or can immediate access to the PMF be requested Proposed change (if any): – please clarify as this is confusing

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
Pfizer

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall, this draft module (GVP Module II - Pharmacovigilance system master file) is very comprehensive and provides detailed and helpful guidance on the establishment and maintenance of a pharmacovigilance system master file. We applaud the Agency for efforts to provide comprehensive guidance. Further, we appreciate the opportunity to review this document and provide the following comments with the goal of improving, and thereby strengthening, the final guidance.
	We reference the extensive comments made by the European Federation of Pharmaceutical Industry Associations (EFPIA), which we fully endorse, and we also offer the following additional suggestions to improve the Guideline. We would be glad to meet with representatives of the Agency to provide clarification on our comments.
	Since the initialism "PSMF" is introduced in Section II.A. (line 40), it is not necessary to spell out "pharmacovigilance system master file" in subsequent text.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
68-70		**Comment:** It is not always practical to expect the PSMF to be 'located' within the EU. In particular, where the PSMF is to be kept within the MAH as an electronic file, the server that houses the file could be located outside of the EU. The requirement should be that the PSMF is accessible from within the EU. Also, see comment on lines 122-125. **Proposed change:** Revise lines 68-70 to read: "*Irrespective of the location of other activities, the qualified person for pharmacovigilance (QPPV) residence and location at which he/she carries out his/her tasks ~~and the pharmacovigilance system master file location,~~ must be within the EU.* ***The PSMF must be accessible from within the EU***."
70-72		**Comment**: As envisioned, the PSMF is extensive. It would be helpful if an example table of contents is provided for a 'typical' PSMF in the revised module. **Proposed change**: Add an example table of contents for a 'typical' PSMF in the revised module.
122-125		**Comment**: It is not always practical to expect the PSMF to be 'located' within the EU. In particular, where the PSMF is to be kept within the MAH as an electronic file, the server that houses the file could be located outside of the EU. The requirement should be that the PSMF is accessible from within the EU. Also, see comment on lines 68-70. **Proposed change**: Revise to read: "*The pharmacovigilance system master file shall be ~~located~~* ***accessible from***

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		within the EU.”
165		**Comment**: The legislation does not state where any CAPA plans are to be located, and MAHs should be allowed flexibility in relation to this, in order to manage their particular circumstances in the most efficient and effective way. **Proposed change**: Revise to read: “*The types of changes that should be routinely and promptly notified to the QPPV are:* *the ~~addition~~ **creation** of corrective and/or preventative action plans ~~to the pharmacovigilance system master file~~ (e.g. following audits and inspections) and managed deviations from the processes defined in the quality management system for pharmacovigilance;”*
297 – 300		**Comment**: On line 298 ‘*Significantly delegated activities*’ should refer to significantly delegated pharmacovigilance activities. **Proposed change**: Revise lines 297-300 to read: “*The pharmacovigilance system master file should also contain copies of signed agreements for significant delegated **pharmacovigilance** activities, such as:* • *“pharmacovigilance service provision (QPPV, safety data entry, PSUR writing, electronic ICSR reporting, evaluation of safety data, etc.);* • *“delegation concerning the pharmacovigilance system master file.”*
484-487		**Comment**: For an MAH with a large and complex PV system, current /continuous updates are not feasible or practical. **Proposed change**: Revise lines 486-487 to read: “...*and to have robust processes in place to continuously be*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		informed of relevant changes in order to revise the pharmacovigilance system master file accordingly. ***The pharmacovigilance system master file should be assessed at least quarterly for updates****. In addition, changes ...”*
515-520		**Comment**: For an MAH with a large and complex PV system current/continuous updates are not feasible or practical. **Proposed change**: Revise lines 515-520 to read: “*The information shall be succinct, accurate and reflect the current system in place, which means that whatever format is used, it must be possible to keep the information ~~continuously~~ up to date and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements [IM Art 5(1)].* ***The pharmacovigilance master file should be assessed at least quarterly for updates.*** *Although provision of the document within 7 days of request ...”*

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

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 II – Pharmacovigilance system master file.
	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')*
175		Comment: II.B.3. The representation of pharmacovigilance systems Please provide a template. Proposed change (if any):
228		Comment: When a pharmacovigilance system is shared, is advised that the partners… Proposed change (if any): When a pharmacovigilance system is shared, it is advised that the partners…
287 - 301		Comment: This information changes on a nearly daily basis: Is it appropriate to list general information on organisations in a table and record details in separate documents (e.g. contracts, agreements, etc.)? Proposed change (if any):
291 – 292		Reference: "…service providers (e.g. medical information, auditors, patient support programme providers, study data management etc.),…" Comment: The activities performed by the example service providers given in the brackets are not pharmacovigilance obligations, hence inappropriate

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): Replace examples by service providers performing e.g. case management, expedited reporting, aggregate report preparation, signal detection etc.
301		Comment: Please provide clarification on "delegation concerning the pharmacovigilance system master file"
309		Sources of safety information should also include a current list... Proposed change (if any): Sources of safety information should be linked/should refer to a current list...
327		nature of testing… Comment: Please clarify
406		not only staff within pharmacovigilance departments but also any individual that may receive safety reports. Comment: This is not consistent with Module I, see lines 194 - 198
417		should also contain a note associated with any audit where significant findings are raised Comment: Please define "any audit", do you mean only received audits or also conducted audits?
519 - 522		Although provision of the document within 7 days of request by a competent authority is stated in the Article 23(4) of Directive 2001/83/EC, marketing authorisation holders should be aware that immediate access to 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 may also be required by the competent authorities. Comment: This restriction is not covered by Article 23(4) of Directive 2001/83/EC and should therefore be harmonised.
523		II.B.6.1. Format and layout Comment: A template would be most helpful

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	I am confused as to why there is so much emphasis on the physical location of what will be an electronic document. Auditing module is not thought out, will decrease effectiveness of audits.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 122-125		Comment: Disclosure of the home or insecure office addresses of contract QPPVs is not acceptable as this will put individuals at risk of physical harm from animal rights activists or customers with a grievance against the company. This would also allow companies who outsource data processing outside the EU to name their main EU site rather than smaller affiliates who handle parts of the process. Proposed change (if any): Preferred wording would be: "...shall be located within the EU, either at the site from which the main pharmacovigilance activities are managed or at the site when the QPPV operates....."
Lines 138-139		Comment: Default to the QPPV address is not acceptable for the reasons stated above, unless this address is not published. Proposed change (if any):
Lines 143-147		Comment: Implies that there will be different PSMF numbers for different licence applications, as for DDPSs. Surely there will only be one PSMF number? How will companies who have old products and who have never needed a DDPS make the transition to the PSMF? If they put in a variation, what will they be varying?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		If the PSMF is prepared for a new application or renewal of an existing licence and there is only one system, does a bulk variation have to be submitted at the same time for all existing products? Proposed change (if any):
Lines 208-216		Comment: Proposed change (if any): Preferred wording would be "....either the site from which the main pharmacovigilance activities of the market authorisation holder are managed or the site where the QPPV....." etc.
Line 263		Comment: Why does the postal address of the QPPV need to be disclosed? Is the EMA intending communicating with QPPVs via this route? Proposed change (if any):
Lines 398 - 429		Comment: The section intent is clear you want quality systems to be transparent, however in reality you will ensure that internal audits only find minor findings and those with critical or major findings never have an audit report issued with findings. If you want the intent to be implemented then don't leave legal holes for people to abuse, it will make auditing harder I get enough grief issuing major findings as it is, with the new legislation this won't happen. List of audits should be only for the last four years; does it include other agency inspections?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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):
Line 463		Comment: Please clarify when the 10 year period for completed audits starts - from July 2012 or from July 2002 - July 2012 initially Proposed change (if any):
Line 519		Comment: Please clarify if PSMF is to be available within 7 working days or 7 calendar days of request. Proposed change (if any):
Lines 575-596		Comment: Expectations regarding MAH legal rights when a thorough review is being performed should be respected. MAH should be informed when a review takes place, and given a time for a response e.g. 2 months. We had a regulatory body wait 7 months to issue an audit report... That's a long time to wait. Proposed change (if any):
Lines 634-636		Comment: Why do the public need to know the location of the PSMF? If this is located at the site of a contract QPPV, which may be a home address or an unprotected office, then personal information will be disclosed. Is this compatible with data protection laws? Once the information becomes available, terrorist organisations such as Animal Rights activists are likely to publish the information widely. In recent years in the UK, these activists have concentrated on "soft" targets, such as suppliers to the pharmaceutical industry, as these do not have

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		the security systems of the major companies and are more accessible. Animal Rights activists do not confine their activities to nuisance letters or phone calls and publication of the home addresses of contractors could lead to damage to property, and more importantly, to physical violence. Publication of this information will also provide dissatisfied customers with somewhere to go to vent their frustration. It is likely that SME who would normally contract out QPPV activities to a suitably qualified external person will be unable to find anyone willing to provide these services. Proposed change (if any):

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19.04.2011

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
la Roche

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Roche supports the comments EFPIA has sent in. The modules are in general well written but would benefit from consistency checks across in terms of definitions and requirements for the quality system. In particular Module I describes that, in each module, particular quality aspects will be discussed, and as this is clearly the case in a number of modules, it is less obvious in other modules. A few additional comments are provided below. The need to include copies of signed agreements into the PSMF was deleted from the implementing regulation. We would suggest to delete this requirement from the GVP. Also the scope in the GVP module is much broader than the implementing regulation; therefore we recommend to align the GVP module with the implementing regulation.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
267		Comment: Section II.B.4.2 and II.B.4.3. contain very similar requests. II.B.4.2. (section on the organizational structure) requires a description of sites where the PV functions are undertaken covering ICSR collection, evaluation, safety database entry etc. II.B.4.3. (section on sources of safety data) requires a description of the main units for ICSR collection (global and affiliate offices) including country, nature of activity and the product(s). The implementing regulation does not contain a section on sources of safety data anyway and the list of contractual agreements is only listed in the appendix, which seems to make more sense. Recommendation: Include the above ICSR section from II.B.4.3 into Section II.B.4.2?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 Apr 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

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
	A general template issued by the Agency would be very appreciated.

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')*
52-53		Comment: "…no requirement for variations for changes in the content of the PSMF" is the contrary to lines 113-116. Proposed change (if any): content of lines 113-116 has to be adapted.
113-116		Comment: Variations should only be mandatory if information on the marketing authorisation changes and not if information in the PSMF is changed. Proposed change (if any): accordingly to comment
125-132 147-149		Comment: As any change of the location of the PSMF is entered in EVMPD, the submission to national competent authorities as a variation is redundant. Proposed change (if any): Submission of variation should be waived.
417-419 421-425		Comment: The request should be removed to keep the benefit and quality of audits. Proposed change (if any):
443-447		Comment: List of MAs is automatically generated and does not contain information on RMPs, etc. This information would have to be added manually, nearly impossible to be kept up to date on our abt. 30,000 MAs. Proposed change (if any):

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17.04.2012

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

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
	Should the change from DDPS to PSMF be made via variation?
	If there are differences between DDPS and PSMF should they be submitted as variation e.g. there will be new QPPV in MAH and her details will be contained in the new PSMF. Is it enough to submit details in PSMF with new product application or should the variation be made?

17.04.2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
SciencePharma

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	May one MAH have more than one QPPV's? Should they all or any of them be employed by MAH?
	Should at least one QPPV be employed by MAH?
	Does QPPV is ascribed to PSMF or to MAH?
	Could you please explain whether it is possible that different products from the same therapeutic group belonging to a single MAH were included in different pharmacovigilance systems (of course described in different PSMF's) (v 187)?
	Could you please confirm that (according to 258) tasks delegated by QPPV to other persons should be described in PSMF and these particular persons listed by name and surname?
	Could you please explain how detailed should be the list described in v 291, should it describe also for example IT service?
	Could you please specify what kind of changes in PSMF should be submitted as variations? For example: (a) should the ending of a study be connected with variation submission, (v 312-316); (b) should the changes in pharmacovigilance procedures be submitted as change to the PSMF (v363-365) (c) should a new product included into pharmacovigilance system be also the reason of submitting change to the PSMF (v173)?
	Could you please specify the metrics mentioned in v 373-375?
	Could you please explain if the number of people involved in pharmacovigilance should be exact or estimated? Should they be listed by name and surname?(v 399)
	Could you please explain (or give an example) of processes described in v 404?
	May excel be used as database and if yes how the validation should be confirmed?

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.

<Date of submission>

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The new legislation requires the submission for variations for certain type actions: Change of QPPV, Change of location of the master file, PSUR DLP 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. 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. The requirement for the variations can all be legally solved by removing the QPPV, location of the PSMF and the PSUR schedule and periodicity from the definition of "conditions for the MA".
	As described in the Implementing Measures, the Pharmacovigilance System Master File (PSMF) contains a detailed **description** of the pharmacovigilance **system.** This means that according to the definition, detailed listings on MA's, contracts etc. are exempt from the definition. These lists are changing several times a day and therefore can never be part of a "document" which has continuously to be kept up to date and should be "permanently and immediate available for inspections at the storage site". Such documents should only be available for review during inspections etc. Therefore we propose to change the "continuous" into quarterly updates and to delete the Appendices but to have these available on request during inspections.
	The document is very extensive and although very detailed will give room to a lot of different explanations and expectations. A template for the PSMF should be provided to avoid long assessment times and discussions over the type of information to be

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

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')*
52-53		Comment: The sentence "This summary includes information on the location of the Pharmacovigilance system master file" may be omitted as is repeated Proposed change: Delete the repeated section.
58		Comment: A close bracket should be included after "2010" Proposed change: Add the bracket
92-96		Comment: This paragraph is not clear. Proposed change: Reword the paragraph to clarify the objective
102-111		Comment: A template would be helpful to avoid variation in requirements between Member States. Proposed change: Add template to annex III of the GVP

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
122-125		Comment: This paragraph is clear when the PSMF is a paper based format. However, if a MAH has a PSMF in an electronic format, the meaning is unclear. Proposed change: The *location of the pharmacovigilance system master file does not mean a physical location but it means the presence or accessibility of electronic documentation, ,* either the site where the main pharmacovigilance activities are performed…….
148-154		Comment: For the variations as needed for the change of the location of the PSMF we refer to our general comment. The location will be in EVPRM database and with that available per licence for every member state. It is bureaucracy and waste of community money to spend time on handling these useless variations. Proposed change: Delete these lines and replace by. "The MAH shall update the EVPRM database with the location of the PSMF for each product"
172-173		Comment: The QPPV already submits a signed statement with the application submission to declare that the MA holder has a QPPV. This means that the signed acceptance of products as referred to in line 173 is redundant since such a statement is already available Proposal: delete line 173
186-188		Comment: When two or more marketing authorisation holders share exactly the same PSMF since they belong to 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')*
		same group, one combined PSMF should be sufficient for both. There is no need for a single and specific master file, which is only confusing. The list of applicable MAHs for which the system is valid is mentioned in the PSMF. Proposal: add as additional sentence: *If two or more marketing authorisation holders share exactly the same system their PSMF can be combined.*
255-257		Comment: A list of countries where the nomination of a local contact person is required should be added. Proposal: Add the list of countries for which a local contact person is required.
296		Comment: the words in this line do not belong to the sentence Proposal: Delete: ~~And the list provided in the Annexes~~
337		Comment: it is unclear what is meant by "the nature of the data held". The example given is not helpful Proposal: Provide a better explanation or example
366 - 386		Comment: A good quality management system results in a good performing pharmacovigilance system. Proposed change: The performance of the Pharmacovigilance system should be moved so that it comes after the section on quality (II.B.4.7)

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
367		Comment: monitoring compliance and with that the performance of the pharmacovigilance system is an ongoing process. Reports should be available, however to then require the evidence" of those reports in the PSMF is disproportionate. The system should be described and the outcome of the system should be reviewed in inspections. Proposal: The PSMF should contain ~~evidence of the ongoing~~ *a description of the* monitoring of the performance of he pharmacovigilance system including the compliance of the main outputs of pharmacovigilance.
374		Comment: What information provided by competent authorities is referred to here? Proposal: Clarification needed.
395		Comment: There is no need for the MAH to have the SOPs and other procedures of service providers or other third parties. Other then that these SOPs are confidential documents and only to be reviewed on site. There are PhV agreements with those partners. Audits are conducted to check whether these agreements are followed. In case of non compliance additional training/audits etc are conducted. There is no added value of having and maintaining a list of procedures of service providers and other third parties. Proposal: Deleted the requirement for listings the SOPs for service provides and other third parties.
398 - 404		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 lines don't refer to the PhV training. Proposed change: Create a separate sub-section which may be called "PhV organisation structure"?
404		Comment: it is not clear what instructions on critical processes means. Proposal: Clarification is needed
420-424		Comment: "Preventative" is incorrect Proposal: replace preventative by *preventive*
432		Comment: In a generic medicines company with about 30.000 licenses "a list of medicinal products" is outdated the moment it is printed. Therefore to have this continuously annexed to a document makes no sense, since it would require the log to be updated with every change in license/contract etc. All licenses in the EU of a MA holder are available in the EVPRM as of July 2012 so there is no need for separate provision. The list of MAs should therefore NOT be part of the PSMF.
443		Comment: A list of products authorised in the EU cannot contain products authorised outside EU. Proposal: deleted requirement to list product authorised outside of EU.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
484-488		Comment: In a generic company the product list changes on average 10 times a day. It is indicated in these lines that change control systems are needed and records should be maintained for that. The product portfolio will be kept updated in validated databases. These validated databases do have and audit trail for which all can be followed. The list as to be generated when needed for the PSMF will in general not be "printed" and can therefore NOT have any change control. Proposal: Lines 484 to 489 should be deleted since the provision as described above on the validated systems is described in lines 490-500
567-569		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. 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.

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
MHRA

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	• The implementing measures text contains a clarification that the **logbook** does not apply to various sections of the PSMF (which is welcomed) and that version control is necessary, the text remains in article 6 (4) record 'any alteration' of the content. This means that any change to the list of documented procedures and processes (Article 3 (5) a and b), or the description of human resource with 'number of persons involved in PV activities, the list of sites where they are located' is subject to 'logbooking' because these items are not in the Annexes. This is potentially burdensome upkeep activity for MAHs, the list of procedures should be removed to the Annexes and staff numbers and location needs to be in the annex, or otherwise accompanied by a clarification that this does not need to be addressed in the logbook. Section II.B.4.7 will need to be revised pending the final IM text. • It is also noted that the IM text contains, in the content of the PSMF, a list of sites where persons involved in PV activities is not necessarily required as part of the PSMF. It came from the 'resource management' in the QMS GVP and ideally resides in the QMS system as part of resource management and training area. The organisation chart described in 5 b is a repetition of the article 3 (2) description of the organisational structure and could also be removed. The final IM text is required in order that this can be clarified in the GVP.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	• What are the 'critical processes' in section II.B.4.7 ? This has been taken from the QMS GVP and appears to be repetition of section II. B.4.5 (processes) • The other areas affected by the **logbook** text in the IM is the list of subcontractors (delegated activities) in Article 7 (2), which **should be in the Annexes.** The *description* of the delegated activities has been removed, which is important to retain in GVP, because otherwise there is simply a list of contracts, the products and territories but not the actual activity (e.g. database entry as a service). • The article numbers have changed in the IM and some items have been removed (CAPA, 7 day provision of the PSMF) so the GVP module requires re-referencing	

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)*
78-79		Comment: Word change The pharmacovigilance system master file provides an overview of the pharmacovigilance system, which may be requested' This may imply that the system rather than the master file may be requested Proposed change (if any): The pharmacovigilance 78 system master file provides an overview of the pharmacovigilance system, ~~which~~ **and** may be requested'	
105		Comment: Word change 'The Member States in which the qualified person resides and carries out his/her tasks' This implies that the QPPV can reside/carry out their activities in multiple Member States Proposed change (if any):	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		The Member State~~s~~ in which the qualified person resides and carries out his/her tasks	
112-113		Comment: Word change Proposed change (if any): 'for submission of a detailed description of the pharmacovigilance system (DDPS) with each marketing authorisation application is ~~not~~ **no** longer applicable.'	
126		Comment: The text of the implementing measures does not appear to specify initial notification of the location of the PSMF in database or via any other route, but references changes only. In addition, the Directive does not appear to state that the (article 8 summary) location must be provided for those products that do not undergo renewal or approval from 2012. MHRA have fed this back via the comments on the implementing measures text. What is the legal basis for requiring the PV system summary submissions for these products? Currently the new legislation only states that PSMF must be available for products without a DDPS and with unlimited validity. This should be clarified in the GVP.	
130		Comment: Transition topic	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		Pending the full population of the database by Industry and EMA, NCAs will have to share information about variations submitted. It will need to be decided and communicated how this will work; for example if a variation is submitted for a nationally authorised product and describes other products under the PSMF for which variations have not been submitted - what are expectations concerning residual DDPSs? What if a CAP is included under a PSMF made known via a national variation - does the supervisory authority remain as the QPPV site until the CAP is varied or change to the new country? This needs to be covered in transitional guidance if not in the GVP.	
141-145		Comment: 'Once the database referred to in Article 57(1)(d) of Regulation (EC) No 726/2004 is functional, all pharmacovigilance system master files will be registered in EVMPD and a unique number assigned.' 'At the time of marketing authorisation application, the applicant should apply for, and subsequently include in the application, the pharmacovigilance system master file reference number, generated by EVMPD. ' This section is confusing. The section states that applicant must apply for a PSMF number (generated from the article 57 database) and that this is relevant in other situations once the database is functional. This implies that if applicants are required to include the reference number the database *must* be capable of generating a number from July. Therefore is the first part of line 141 relevant? Should it start	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		at 'all pharmacovigilance system master files will be registered….'? Proposed change (if any): ~~Once the database referred to in Article 57(1)(d) of Regulation (EC) No 726/2004 is functional,~~ All pharmacovigilance system master files will be registered in EVMPD and a unique number assigned.	
141-145		Comment: Transition topic The variations classification guideline currently in draft requires a PSMF number. How will this be allocated without the article 57 database? Do Member States need to assign a unique reference or do MAHs need to be told how to do this?	
174		Comment: Clarification 'transfer of responsibility for a pharmacovigilance system to a QPPV' This refers to the receiving QPPV not the outgoing QPPV Proposed change: 'transfer of responsibility for a pharmacovigilance system to a	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		new QPPV'	
178		Comment: Text removal The start of this sentence is duplicating the first bullet point and also implies that this is the only circumstance where different PV systems may be applied which is incorrect. The different categories of products is only an example and not the only appropriate circumstance Proposed change (if any): ~~For different categories of medicinal products~~ **T**he marketing authorisation holder may, if appropriate, apply separate pharmacovigilance systems. Each such system shall be described in a separate pharmacovigilance system master file.	
375		Comment: Missing word Proposed change (if any): An overview of the timeliness of PSUR reporting **to** competent authorities in the EU	
401		Comment:	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		'listing of sites where the personnel are located' Unknown why this sentence has been included. It appears to have been copied from the QMS GVP however the reason for inclusion in the context of the PSMF is unclear. Proposed change (if any): Remove sentence	
402		Comment: Missing word Proposed change (if any): including a reference to the location **of** training files	
404		Comment: 'instructions on critical processes [IM Art 213(4)]' Unknown why this sentence has been included. It appears to have been copied from the QMS GVP however the reason for inclusion in the context of the PSMF is unclear. Proposed change (if any): Remove sentence	
436		Comment: Spelling mistake	

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

Please add more rows if needed.

<18 April 2012>

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

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*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Both the Regulation and the Directive are aiming for increased patients safety, reduction of bureaucracy and enhanced transparency. In parts the proposed module seems to miss those aims as is generates multiple requirements for storage and maintenance of essentially similar data without adding to patient safety or transparency. It is recommended to reduce the required dataset to the absolute minimum to enable the focus on improving patient safety and transparency whilst reducing replicated 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')*
104, 105,106, 110		Referencing these lines please add a new line after line 110: "A *reference to the PSMF registry number / QP registry number would be adequate"*. Reference is made to a CMDh recommendation presented at EGA workshop London, January 19-20, 2012 Please see comment to lines 139ff as well.
114-117		Comment: It is understood that both on the Regulation level (Art 16) and the Directive level (Art 23) – both referring to Dir Art 8(3) which among others requests that the MAH shall provide the Agency and the NCAs with any new information – provision of any new information on both the contact details of the QPPV and the location of the PSMF is mandated. Retaining the need for a variation if changes to the summary of the PV system are made is inefficient and places a bureaucratic burden on both Regulators and the Industry. The location of the PSMF and the name and contact details of the QPPV are required to be submitted to EVMPD in accordance with Article 57 and will accordingly updated therein as appropriate. This procedure is precisely outlined in line 608ff, is rightly described as "a practical mechanism" and should be fully sufficient. Therefore, it is suggested that individual product variations should not be necessary and this requirement be removed. Proposed change (if any): If this proposal is followed, the following lines need to be amended, because they all refer to the need of a variation: 113-115, 130-131, 148-154 and 567-569
125-132, 139ff		Comment: While it is agreed that the PSMF location is a relevant information in the PSMF registry within EVMPD 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')*
		change of this information is not relevant to single licenses. The need for variations to all NCAs should be removed. The details in the MA won't change as the reference to the PSMF registry number stays unchanged (see comment to lines 104 to 110).
147 - 153		Comment: Why is a formal variation process needed and in parallel the registration in the EVMPD for master file location information? As for the purpose to understand at any time where the PSMF is located the reference should be the EVMPD. Proposed change (if any): Delete the requirement for variation and include that for any change the MAH is responsible to update the EVMPD in due time. EVMPD must be correctly populated with the pharmacovigilance system master file location [IM Art 3(2), Art 5(3)]. The marketing authorisation holder is responsible to update EVMPD in due time when location changes of the pharmacovigilance system master file occurr.
172-174 (173)		The QPPV should explicitly accept the following changes in writing: - inclusion of products into the pharmacovigilance system for which the QPPV is responsible; Comment: If this requirement holds on both the EEA level and the product level (i.e. each new strength, form of administration etc.) this may be quite cumbersome and administrative. It would be less administrative if this requirement referred to the active moiety level ("active moiety" instead of "products"). It is understood that the QPPV will have oversight on all products by cooperation with both the regulatory affairs groups and third parties. 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')*
		Removal of the above mentioned bullet point "inclusion…"
204 – 206		Comment: The overview of all PSMFs should be created from the EVMPD to avoid that any change in any one PSMF creates the necessity to update all other existing PSMFs. Proposed change (if any): Delete this requirement or refer to a management report in EVMPD.
297-301		Copies of agreements should not be part of the PSMF because this contravenes the key concept that the PSMF should be succinct (as described in II.B.6 in line 516) and presents duplication of information located elsewhere with the MAH. At present this also represents a conflict with lines 457-458 of this GVP module which refer to a list of contracts.
308-315		Comment: It is believed that the request to include and maintain a current list of all studies, registries, and surveillance or support programmes does not add value to the PSMF as most of this information is either known through approval procedures with the authorities and/or is presented in detail in the respective periodic safety update reports provided to the authorities on a regular basis as long as relevant safety information results from such sources. The PSMF provides sufficient detail that MAHs have systems and processes in place to collate and collect safety reports from all sources relevant to their products and it does not add any value to maintain a highly administrative list of current studies, registries, surveillance support programmes incl. their respective status as requested in this section. In addition there are no globally accepted clear definitions of what constitutes a surveillance or support

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		programme or what is considered to be a non-interventional study which would result in significant inconsistencies and different interpretations. Therefore, to avoid unnecessary duplication of efforts, and ensure adequate use of resources it is suggested to delete lines 308 to line 318 completely. It is acknowledged that the MAH has the responsibility to ensure that ICSRs from all sources have to be captured and analysed as outlined in the other GVP modules and these processes are sufficiently displayed by referencing SOPs and contractual agreements, respectively.
372-375		More clarity on what 'quality of submissions' and 'performance of pharmacovigilance' means and how they can be measured would be desirable.
383-385		More clarity on the term 'targets for the performance of the pharmacovigilance system' would be desirable. Also more clarity on performance indicators is needed. Per the Concept Paper (B 11.) MAHs *may* use performance indicators. In contrast to that , the GVP modules now requests that "a list of performance indicators *must* be provided". Given this is a stricter requirement guidance would be valuable. It is understood that per the Concept Paper EMA may publish a list of such indicators.
404		More clarity on the term 'critical processes' may be desirable. This might refer to the areas listed below line 370, i.e., ICSR reporting, PSUR reporting, safety variation submissions and fulfilment of commitments, other obligations and conditions.
422-426		Further clarification is required about the "independent verification" of corrective action or significant improvement.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
430-442		The main part of the list should be available from EVMPD anyway. Duplicate data collection and maintenance is an unnecessary administrative burden and source of mistakes. It is beneficial for both the authorities and the companies to reference to EVMPD for the data available there and not hold the data in addition as a copy in the PSMF Annex. Proposed change (if any): It is recommended to update the list not more often than once a month unless a new active moiety needs to be included.
443-447		Comment: The need to indicate within the product list what type of product specific safety monitoring requirements exist eg risk minimization measures, non-standard PSUR periodicity may present a practical problem. As the list is likely to be generated from a controlled system it is very unlikely that this additional information is available from the source system. Addition of these incremental requirements to the list would therefore be a manual process that would be highly impractical. It is therefore proposed that the Annex to the PSMF may contain additional lists that are more easily maintained e.g. a list of products with RMPs, list of products with specific safety monitoring requirements (adverse events of interest). We believe that the PSMF should describe the PV system but not include product specific outputs of the system therefore cross-reference or links to the product specific information should be sufficient.
462		Clarification is needed as to whether this is applicable for external delegation only. If not would delegation to a department be sufficient?
463		It is felt that the requirement for audit history over the preceding 10 years is not practical or relevant, due to changes in legislation and practices over such an extended time period. The Concept Paper for the IM contains

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		the following: The master file shall contain a logbook recording any alteration of its content within the last five years. This logbook should record the date, the responsible person and where appropriate the reason for the alteration. Proposed change (if any): In line with the Concept Paper we suggest a 5 year history of audits would be appropriate.
468-470		More clarification regarding the 'logbook' appears desirable.
472		The PSMF as described in this module including the annexes would be a constantly changing system impractical to work with. To enable change control, versioning and working with the system the addition of the following sentence is recommended: *The frequency of updating any parts the PSMF itself as well as the annexed documents should be risk based determined and documented in the PSMF.*
530		Comment: Language of the PSMF It is defined as "should" that the language for the PSMF is English only and that the MAH is not required to maintain multiple versions of translated PSMFs. It should be clearly specified that there is only one version in one language Proposed change (if any): The pharmacovigilance system master file shall be written in English only (unless the marketing...

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
Vigilex b.v. Oudedijk 9b 3062 AB ROTTERDAM Tel.: +31 (0) 10 244 7399 Fax: +31 (0) 10 244 7319 Mail: info@vigilex.com

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

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

1. General comments

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

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')*
172		Comment: QPPV should explicitly accept the changes in writing: inclusion of products. For big pharmaceutical companies, this will imply that the QPPV has to sign updates daily. Proposed change (if any): • inclusion of new compounds (excluding new formulations, indications or brand names)
303		Comment: ICSR Proposed change (if any): Safety Information
333, 390		Both sections describe the need of having clear documented procedures. This is confusing and seems like duplication. Proposed change: integrate the two paragraphs into one
399		Comment: Resources management: number of people involved in org. chart. This may be an unrealistic request as number of staff may change depending on the activities at hand. E.g. for the preparation of a PSUR or end of study reconciliation activities. Additional resources may be hired. How do you capture these "flex" resources? Proposed change (if any):
Line 165, 417, 419.		In the PSMF must be a note of critical findings and a summarized CAPA including deadlines. What is a note? Is stating that 1 critical finding was observed, a note?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Does the list have to include internal audits only, or also audits by partners and/or inspection findings? and the corrective and 419 preventative action plan (with deadlines for completion) for these findings will be summarised Some additional guidance will be appreciated. E.g. is stating "a corrective and preventative action related to compliance will be completed by 30 august 2012", enough? Proposed change: please provide more details on what is expected
462		A list of completed audits for the last 10 years, and a list of audit schedules. For a small or merged company, this may be impossible to realize. Explain, only PV audits or all GXP audits?
536, 309, 431, 458		In general embedded documents are discouraged. overview of studies overview of products overview of contract These are typical overviews that may change frequently. For big companies, such data will be available in databases. Proposed change: to allow MAH to extract such data at the time of submission/request. The PVMF, only refers to the source/database.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module II – Pharmacovigilance system master file' (EMA/816573/2011)

Comments from:

Name of organisation or individual
Zeincro Hellas S.A.

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

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

1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 126-132		Comment: A full stop has to be omitted in line 130. Proposed change (if any): "Details about the location of the pharmacovigilance system master file are required to be entered in the Eudravigilance Medicinal Product Dictionary (EVMPD), and any change to the location shall be notified immediately to the Agency in order to have the information in the database referred to in Article 57(1)(d) of Regulation (EC) No 726/2004 and on the European medicines web-portal updated [IM Art 5(3), REG Art 57(2)(c)] (cross ref Eudravigilance and EVMPD guidelines), as well as submitted to national competent authorities as a variation in accordance with Commission Regulation (EC) No 1234/2008 and the associated Guideline."
Line 127		Comment: Throughout the document there are different references to the medicinal product dictionary, either as EVMPD (in lines 127, 130, 142, 145, 146 and 153) or XEVMPD (in lines 211 and 217). A consistent reference (as XEVMPD) is recommended. Proposed change (if any): Line 127: "the Extended Eudravigilance Medicinal Product Dictionary (XEVMPD)". The "EVMPD" reference in lines 130, 142, 145, 146 and 153 should be also changed to "XEVMPD".
Lines 134-139		Comment: A rational for the location of the PSMF is described. According to that rational, location of the PSMF at the site where the QPPV operates would be applicable only in situation where the main pharmacovigilance activities take place outside the EU, or where a main site cannot be determined. We consider that this has to be clarified (or at least referenced to) in lines 48-50, lines 122-125 and lines 209-213. Proposed change (if any): Lines 48-50: "The pharmacovigilance system master file shall be located either at the site in the EU where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site where the qualified person responsible for pharmacovigilance operates (see II.B.2.2.)

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		[IM Art 3(1)].” Lines 122-125: “The pharmacovigilance system master file shall be located within the EU, either at the site where the main pharmacovigilance activities are performed or at the site where the qualified person responsible for pharmacovigilance operates (see II.B.2.2.) [IM Art 3(1)], irrespective of the format (paper-based or electronic format file).” Lines 209-213: “The address of the location of the pharmacovigilance system master file provided to fulfil the requirement of Article 8(3) of the Directive 2001/83/EC (and within XEVMPD) should be an office address which reflects either the site in the EU where the main pharmacovigilance activities of the marketing authorisation holder are performed or the site where the qualified person responsible for pharmacovigilance operates (see II.B.2.2).”
Line 183		Comment: A square bracket has to be omitted in line 183. Proposed change (if any): “[IM Art 2(2)]”
Lines 208-216		Comment: Provision for location of the PSMF is already described in lines 126-139. Proposed change (if any):”Submission of summary information to competent authorities cannot contain multiple locations for a single pharmacovigilance system master file.”
Lines 250-251		Comment: Text in lines 250-251 must be bulleted. Proposed change (if any):
Lines 261-267		Comment: The details provided in relation to the QPPV which are described in lines 261-263 are already listed in the lines 250-251. It would be more clear and straightforward to amend provisions in lines 250-251 and omit details in lines 261-263.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): Lines 250-251: "a summary curriculum vitae with the key information on the role of the qualified person responsible for pharmacovigilance, including description of the QPPV qualifications and experience, as well as proof of registration with the Eudravigilance database;" Lines 261-267: "The contact details supplied should include name, postal, telephone, fax and e-mail and represent the usual working address of the QPPV, which may therefore be different to a marketing authorisation holder address. If the QPPV is employed by a third party, even if the usual working address is an office of the marketing authorisation holder, this should be indicated and the name of the company the QPPV works for provided."
Line 291		Comment: A semicolon has to be replaced with colon. Proposed change (if any): "according to: service providers"
Lines 294-296		Comment: The text in line 296 "and the list provided in the Annexes" is not connected meaningfully to the sentence "Individual [...] and audit [IM Art 7(3)]" in lines 294-295. Please review the text. Proposed change (if any): "Individual contractual agreements shall be made available at the request of national competent authorities and the Agency or during inspection and audit [IM Art 7(3)]. The list of these agreements shall be provided in the Annexes of the PSMF (see II.B.4.8.).
Line 376		Comment: The preposition "to" is missing in line 376. Proposed change (if any): "an overview of the timeliness of PSUR reporting to competent authorities in the EU"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 383-386		Comment: Provisions in lines 383-385 and in line 386 are similar. We propose that the line 386 should be omitted. Proposed change (if any):
Lines 393-396		Comment: Provision for listed procedures and processes including the effective date would lead to onerous need for updating the PSMF section on quality system. Effective dates are changing following regular review of the procedures and processes and we consider that updating the PSMF with new effective dates has no added value to the GVP. On the other hand, It might be informative to list the date that the first version of each procedure and process came into effect. Proposed change (if any): "The list should comprise the reference number, title, date of effect of the initial version (for all standard operating procedures, work instructions, manuals etc.), and a description of where the documents can be accessed. Standard operating procedures belonging to service providers and other third parties should be clearly identified."
Line 480		Comment: The preposition "of" is missing in line 480. Proposed change (if any): "organisational changes, such as takeovers or mergers of the sites at which pharmacovigilance is"