EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2012
EMA/428922/2012
Patient Health Protection

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

GVP Module VIII – Post-authorisation safety studies

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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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
AESGP

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

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
	Generally the process for voluntary PASS versus imposed PASS is differentiated and the requirements are appropriately tailored. Some sections however are lacking such differentiation. The document would benefit from the addition of a flowchart describing the different pathways for the request of a PASS and review of documents relating to them etc. in order to improve clarity. In addition the section VIII.C.4.2. would be better placed at the beginning of the document in order to provide the context early on.

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')*
54-60		Comment: the language concerning non-interventional studies should be amended to apply to non-prescription medicines as well. Proposed change: - The medicinal product is ~~prescribed~~ administered in the usual manner… - …and the ~~prescription~~ administration of the medicine is clearly separated….
106-107		Comment: Non-EU post-authorisation safety studies not requested by an EU competent authority are out of scope here and this should be made clear. Proposed change: …and conducted outside the EU at the request of an EU competent authority.
108-119		The definition should be consistent with those of Volume 10 and Directive on Clinical trials. We would prefer adding all definitions in the annex I document on definitions in order to avoid inconsistencies.
161-163		As non serious adverse reactions have to be submitted to authorities within 90 days, the provisions should be adopted as the ENCEPP requirements might not be up to date. Receipt of non serious adverse reactions in a PASS as study end or time of CRF completion may result in work overload in a short timeframe and delay of identifying potential signals. Proposed change: provisions for meeting the marketing authorisation holder's pharmacovigilance obligations, including the reporting of serious and non serious adverse reactions and other safety data by investigators, if applicable
193-195		Comment: The requirements for publication of the PASS Studies should not be more demanding than those for other studies. Proposed change: After "…start of data collection" (Line 194) please add: "Content and data fields mirror

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		those required in EudraCT to the extent possible."
229		Comment: It is not practical to include all milestones in the protocol as these may change frequently and then – due to this requirement – require frequent inappropriate protocol updates. The interim analyses provided will include the requested information. Proposed change: Therefore we propose removal of this requirement.
364-367 (Minor)		Comment: swap the order of the two sentences in this paragraph – it would read more clearly. Proposed change: The marketing authorisation holder shall submit the final study report to competent authorities of the Member States in which the study was conducted [DIR Art 107m(6)]. The study report should be submitted to the competent authority(ies) as soon as possible after its finalisation and within 12 months of the end of data collection.
328 - 331		Line 330 requires further explanation as, for database studies, data are frequently provided to the MAH at preset dates, which may be several months after the event. Proposed change: Any new information that the MAH becomes aware of that might influence….. In addition this sentence is very broad. This could be interpreted as a requirement to immediately report all potential new safety information even if it has a low public health impact and may only lead to a minor labelling update (if any, in case the new information is subsequently confirmed to be not valid or not strong enough to support a labelling change). Proposed change: To avoid that the authorities inappropriately receive many notifications we suggest changing this phrase to "Any new information that might significantly change the risk-benefit balance"
570-605		Paragraph b also derives from article 22a/10a of the legislation and address the need for PASS following the discovery of a safety concern (following regulatory procedure). Paragraph 596-604 applies to this case as well and should be added.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: repeat paragraph 597-605 in section b

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
Allergan Global Safety & Epidemiology

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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')*
41-44		Comment: PASS definition is very broad and could potentially encompass any study, of any design, retrospective or prospective, that includes safety data of any kind. Is this the intention? Please clarify what is in/out of scope. Proposed change (if any):

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

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

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1. General comments

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

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')*
492 - 494		Comment: Will the English translation of the abstract of the Final study report, entered in the register of non-interventional post-authorisation safety studies, be available for the public immediately after entry, or will it become available only after assessment of PRAC / CMDh or NCA? Proposed change (if any):
502		Comment: The term “unjustifiable delays of the publication”needs to be defined Proposed change (if any):
608		Comment: Slight typing error Proposed change (if any): Module VI instead of Module VII
686 - 690 (linked with 492-494)		Comment: Will the PRAC / CMDh / NCA conclusion be published together with the abstract of the Final study report ?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 add more rows if needed.

NOTE A L'AGENCE EUROPEENNE DES MEDICAMENTS

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

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

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

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
Federal Institute for Drugs and Medical Devices (BfArM) Division of Pharmacovigilance Kurt-Georg-Kiesinger-Allee 3 D-53175 Bonn

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Publication of study protocol Article 26 1h) of Regulation EU No. 1235/2010 foresees that protocols and public abstracts of results of the post- authorisation safety studies referred to in Articles 107n and 107p of Directive 2001/83/EC are to be made public. The current wording of the GVP Module encourages the marketing authorisation holder to publish the study protocol but does not include specific information on the publication of protocols or study abstracts or on an obligation to publish these documents. As the obligations laid down within the Regulation would have to be met it is considered more useful to include information on publication of the study protocols and abstracts within the GVP Module and to define the responsibilities for publication.

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 113		Comment: It would be helpful to define the term “analytical dataset”, e.g. as laid down in the “ENCePP Code of Conduct – Implementation Guidance for Sharing of ENCePP Study Data”: *the analytical data set is defined as the minimum set of data required to perform the statistical analyses leading to the results reported for the study and which, together with a complete audit trail describing the manipulation of raw data to obtain the analytic dataset, would be sufficient to allow a third party to repeat or corroborate the results. In principle, this can be raw data, provided this is in line with data protection legislation, or an aggregation of the data. For raw data, the complete audit trail should always be available as well. If sufficient to address the issue based on which access to data is requested, it is acceptable to only make available a subset of the full analytical data.* Proposed change (if any): see above
Line 364-367		Comment: The current wording indicates that the study report should be submitted to the competent authority(ies) within 12 months of the end of data collection and further specifies that the marketing authorisation holder shall submit the final study protocol without providing a timeline. To avoid any uncertainties with this obligation it is recommended to follow the wording of the Directive and to additionally indicate that the marketing authorisation holder shall send the final report to the competent authorities of the Member States in which the study was conducted within 12 months of the end of data collection. Proposed change (if any): The study report should be submitted to the competent authority(ies) as soon as possible after its finalisation and within 12 months of the end of data collection. The marketing authorisation holder shall send the final report to the competent authorities of the Member States in which the study was conducted within 12 months of the end of data collection.

Please add more rows if needed.

13 April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Module VIII is heavily weighted towards NCE “Big Pharma”. RMP assessors are now assessing applications in addition to the pharmaceutical, clinical and non-clinical assessors and the generic industry is concerned that there will be more requirements to do unnecessary PAS Studies. If the generic industry is expected to carry out studies as laid out in the module, then this will mean extra cost which will have to be passed on in the form of higher priced medicines, or fewer companies producing new generics, which will mean less competition and therefore higher priced medicines. A PASS should not be used by regulatory authorities to “force” generic companies to investigate something which has not been investigated by the innovator.
	For many SMEs such large PASS are not an option from a financial point of view. Have the EMA/HMA considered that companies will cancel licenses if requested to do any PASS or PAES?
	This could be used as a barrier of entry to SMEs, by branded and larger companies; thus reducing competition in the market place.

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')*
106, 107		Comment: “should also be considered by marketing authorisation holders” is unhelpful. There is an implication that unless studies are carried out in the same way then there is a risk of them being unacceptable. This should be stated clearly or if outside the scope of the legislation it should not be said at all. Proposed change (if any):
121,122		Comment: generic companies should not be required to carry out studies that have not been required by the innovator. If there is a difference between the innovator and the generic then the study should only address the importance of the difference. “Public Health Importance” is not defined and can therefore be interpreted differently. One person is important but when does something become of Public Health Importance? Proposed change (if any):
126, 127		Comment: This should not be required of generics as the molecule will have been on the market for more than 10 years. What is meant by a “large” population? Is 1000 patients large? Is 100 patients large? Proposed change (if any):
557		Comment: Who justifies the obligation and to whom? If a regulatory agency creates the obligation does the applicant have recourse to object? Proposed change (if any):

Please add more rows if needed.

18. April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall, the document appears consistent with the regulation/directive and very helpful for interpretation. However, not unexpected based on individual viewpoints, there might be some room for further improvement, such as • using more examples? • In section dedicated to non-interventional design, such as VIII.B, being more strict/repetitive in using the term "non-interventional studies" instead of "studies"? • Including an index of relevant terms indicating the pages where they are addressed?
	Topic: Examination of off label use within post authorisation safety studies (as a part of the investigation of the use of a medicinal product in clinical practice). It is recognized that a post authorization study could be initiated as a clinical trial according to Directive 2001/20/EC but an investigation of the use of a medicinal product in clinical practice should be made without any influence of the prescribing physician meaning a non interventional study. According to Vol 9A a PASS was defined as a non-interventional trial for the investigation of the use of a medicinal product in clinical practice without influencing the prescribing and without additional investigations other than those foreseen in the product information. These studies shall be conducted amongst other objectives "…if there is concern regarding the use of the medicinal product (e.g. to quantify the off-label use)…." This is also in line with the ENCEPP Considerations on the definition of Non-Interventional Trials under the current legislative

Stakeholder number *(To be completed by the Agency)*	General comment
	framework (clinical trials directive): " Similarly, the following prospective studies should never be considered as falling within the scope of Directive 2001/20/EC: Studies which evaluate patterns of the usage of medicines, including potential off-label use or measuring the effectiveness of risk management measures in current practice, such as collection of data on drug utilisation and occurrence of health outcomes." The qualitative and quantitative compliance in clinical practice with standards given in the SmPC can only be documented in an observational study, where the use of the product is not determined by an interventional protocol. Since the off-label use is assessed in retrospect by the analysis of the indication for use (normally in the case record form) there is no risk to promote the off-label use within in a post-authorisation safety study. In some European countries like Germany the use of a product outside the approved indication is not permitted in non interventional studies. According to the German Medicinal Products Act (AMG) a non-interventional study is defined in the following way: A non-interventional trial is a study, in the context of which findings resulting from persons' treatment with medicinal products are analysed using epidemiological methods; the treatment, including the diagnosis and monitoring, shall not follow a predetermined trial protocol but shall result exclusively from current medical practice; in so far as a medicinal product requiring a marketing authorisation or a medicinal product requiring an authorization pursuant to Section 21a sub-section 1 is concerned, this shall be conducted, moreover, according to the specifications regarding its use contained in the marketing authorisation or authorisation." So the evaluation of an off-label use within in a post-authorisation safety study, which is/was/will agreed with the EMA is not permitted

Stakeholder number *(To be completed by the Agency)*	General comment
	at the moment. In this context we would like to point out that the German regulation mentioned above is based on Directive 2001/20/EG (Article 2) and is thus also obligatory for the European law. In general we would appreciate if the content of the GVP-Modules would not exceed the content of the Directive 2001/20/EG.

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')*
after Line 65		Comment: Add an advice concerning the decision for using an non-interventional study as explained in the question and answer document. **Proposed change (if any):** Please add the following sentence after line 65: “These trials are typically of a lower risk than interventional clinical trials. This shall ensure that medical activities are normal clinical practice and as such part of the general medical surveillance of a patient.”
Line 66 - 67		**Comment:** Example(s) what would constitute a violation of the non-interventional context would be helpful. Particularly the relevance of drawing blood samples in this context might be difficult to assess?
After Line 67		**Comment**: Add an advice who to proceed concerning the evaluation of off-label use. **Proposed change (if any):** Please add the following sentence after line 67: In case of evaluating the possible off-label use this shall be requested via the case report form field indication
Line 106		**Comment**: The legal basis of this GVP Module for studies developed and conducted outside the EU is not clear

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): The following aspect should be added: …outside the EU, which have been requested by the agency or competent authority These guidance and requirements should also be considered by marketing authorisation holders for studies developed and conducted outside the EU, which have been requested by the agency or competent authority.
Line 114 ff		**Comment:** Substantial amendment in a non-interventional study - an example of e.g. would "NOT" constitute a substantial amendment would be helpful?
Line 147 ff		**Comment**: Here the concept of "Investigator Sponsored (but industry "funded" ..) Studies" is extended to the non-interventional context? This should be made clear and the requirements for NIS should not exceed those as defined for interventional studies? Also, would the QPPV resume responsibility for ADR reporting from these studies.
Line 174 - 186		**Comment:** In this section it is stated that for PASS voluntarily initiated by the marketing authorisation holder, the marketing authorisation holder is encouraged to transmit the study protocol prior to the start of data collection to the national competent authority of the Member States where the product is authorised and to the Agency for PASS concerning products authorised pursuant to Regulation (EC) No 726/2004. The marketing authorisation holder may be required by the national competent authority to submit the protocol to the competent authorities of the Member States in which the study is conducted [DIR Art 107m(5)]. On the other

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		hand, for PASS initiated by the marketing authorisation holder pursuant to an obligation imposed in accordance with Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC, see VIII.C.4.2.. Prior to the start of data collection, the marketing authorisation holder must ensure that information on the study, including the study protocol, is notified to the Agency or the national competent authority, as applicable, and that the Member State in which the study is conducted is informed. That information shall include an English translation of the title and abstract of the study protocol [IM Annex IV.1(4)]. In our opinion it would be more convenient if the core information to be submitted would be the same regardless of whether the PASS has been initiated voluntarily or has been an obligation.
Line 187 ff		**Comment:** The QPPV (e.g. for PASS conducted in Europe) has responsibility for ADR resulting from NIS and thus rather MUST have a final say how they are conducted, particularly for studies planned voluntarily?
Line 309 - 312		**Comment**: The procedure and the involvement of the agency and the competent authorities concerning the change of the classification of a non-interventional trial into a clinical trial should be defined in more detail. **Proposed change (if any):** If changes to the protocol lead to the study being considered an interventional clinical trial the agency or the competent authority should be informed immediately.~~, the study shall subsequently be conducted in accordance with Directive 2001/20/EC and Volume 10 of The Rules Governing Medicinal Products 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')*
		~~European Union.~~
Line 335 ff		**Comment:** E.g. with prospective observational design: Would the authorities encourage to collect AE from which suspected ADR shall be identified via investigator assessment or would generally only an ADR documentation expected? An opinion would be appreciated here, including whether this could be handled differently?
Line 385 ff		**Comment**: With large scale prospective observational studies conducted internationally in general practise: Listing (hundreds?) of names of investigators as part of the study report might appear inappropriate? Could this be restricted to interventional PASS and for observational NIS the respective specialties of physicians could be listed instead?
After Line 461		**Comment**: add the definition of off-label use **Proposed change (if any):** 10.7 Off-label use
Line 466 ff		**Comment:** Examples in the context of a NIS would be appreciated.
Line 496 - 498		**Comment:** In this section it is stated, that for studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the <u>marketing authorisation</u> is encouraged to agree in advance a publication strategy with the principal investigator. In that sentence “marketing authorisation” should be replaced by “marketing authorisation holder”. **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')*
		For studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder is encouraged to agree in advance a publication strategy with the principal investigator
Line 498 - 504		**Comment:** It is recommended that this strategy allows the principal investigator to independently prepare publications based on the study results irrespective of data ownership. In this case, the marketing authorisation holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication, while avoiding unjustifiable delays of the publication. Requests for changes to the manuscript should be based on sound scientific reasons. The marketing authorisation holder should be allowed to require deletion of confidential information In our opinion some information on authorship or adequate references (rules according to the "Vancouver protocol" / European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)) would be helpful.
Line 506 – 508		**Comment:** The marketing authorisation holder is encouraged to transmit the final manuscript of the article to the Agency and the competent authorities of the Member States in which the product is authorised within two weeks after acceptance of the publication. It is not really clear if the document will get published once it was submitted (if so that would be a critical point as "acceptance of a publication" is not always equal with the "publication of the manuscript" itself

Formatted: Justified

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		(potential for a “conflicting interests” which needs clarification).
Line 581 - 595		**Comment:** It is mentioned that if safety concerns apply to more than one medicinal product, the national competent authority or the Agency shall, following consultation with the PRAC, encourage the marketing authorisation holders concerned to conduct a joint PASS [DIR Art 22a, REG Art 10a]. Requests to the marketing authorisation holders should contain the elements of the study design that support the joint proposal. Upon request from the marketing authorisation holders, the national competent authority or the Agency may organise a pre-submission meeting in order to provide suggestions for a joint proposal and facilitate agreement in developing a joint protocol. If a joint protocol is not voluntarily agreed and different proposals are submitted, the national competent authority or Agency may adopt, in consultation with the PRAC, the key elements (for example, the study design and the definition of exposure and outcomes) which each marketing authorisation holder should include in the study protocol. These key elements may then be imposed on all the marketing authorisation holders, pursuant to Article 22a of Directive 2001/83/EC or Article 10a of Regulation (EC) No 726/2004. The study protocols should be implemented within a timescale laid down by the national competent authority or the Agency in consultation with the PRAC and imposed according to Article 22a of Directive 2001/83/EC or Article 10a of Regulation (EC) No 726/2004. Maybe some timelines should be defined.
Line 658 – 659		**Comment:** The study may commence only when the written endorsement from the national competent authority or the PRAC, as appropriate as been issued [DIR Art 107n(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')*
		In that sentence “as” should be replaced by “has”. **Proposed change (if any):** The study may commence only when the written endorsement from the national competent authority or the PRAC, as appropriate hasas been issued [DIR Art 107n(3)].
Line 729 ff		**Comment:** Listing of presented methodology under two main sections: NON INTERVENTIONAL and INTERVENTIONAL (Clinical Trials) might be supportive. Also replacing trial by "study" might add to consistency.
Line 866 – 867		**Comment**: If the study is a clinical trial, provisionss of Directive 2001/20/EC shall apply. In that sentence “provisionss” should be replaced by “provisions”. **Proposed change (if any):** If the study is a clinical trial, provisionss of Directive 2001/20/EC shall apply.
After Line 901		**Comment**: Add information related to the evaluation of off-label use within drug utilisation studies. As also proposed by the ENCEPP Considerations " Drug utilisation studies are useful tools in evaluating the patterns of use of a medicinal product, including capturing off-label use and can be conducted with this specific aim."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): DUS may be used to examine the relationship between recommended and actual clinical practice including capturing off-label use.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11th April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
Centre for Health Evaluation & Research (CEFAR) - National Association of Pharmacies (ANF) – Portugal. CEFAR's mission is to develop high quality research & evaluation studies / analysis that support the development of Portuguese pharmacies, support evidence based decisions in the field of Medicines and Health and advance knowledge in medicines, pharmacy practice and health. CEFAR is member of ENCePP (European Network of Centres of Pharmacoepidemiology and Pharmacovigilance).

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 0) 0 7418 **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 Centre for Health Evaluation & Research (CEFAR) is very pleased to have the opportunity to offer our perspectives and suggestions, and submits for your consideration the following comments on the "'GVP Module VIII – Post-authorization safety studies. We are encouraged that the European Medicines Agency has identified the need for high quality safety post-authorization safety studies and for well-designed tools in order to harmonise the performance of the new pharmacovigilance activities introduced by the amended pharmacovigilance legislation. We find that the document represents highly qualified work and since accomplished, it has the potential to become a very useful tool for all stakeholders within the field. Additionally, we hope that transparency would be a key issue in all post-authorization studies – namely post-authorization safety studies - conducted in Europe. Unequivocally, society demands a transparent and an integrated assessment of benefits and risks, under real life conditions, as the next logical step after clinical trials. Finally, we would like to highlight that community pharmacies can play a special role in collecting data about drug use and its effects in routine clinical practice. Actually, pharmacy-based active surveillance of medicines can contribute as a platform in supporting continuous benefit/risk assessment throughout a medicine's lifecycle under real-life conditions, which encompasses the specific context of post-authorization safety studies. We have no general comments, but a few specific comments are listed below.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
145-147		Comment: EMA has declared its intentions to ensure full transparency of "*relevant*" information pertaining to the study on page 5 (line 145-47), but the specifics about how and by whom are sometimes virtually absent throughout the document. We feel the need that should be described in more detail, including the definition of "relevant" information. Proposed change (if any):
531-541		Comment: A clarification is needed to know if there will be a registration for post-authorization safety studies, not only at European level but also at a national level. With regard to observational studies' registration, there is not a common platform and rules within EU countries often diverge. Moreover, the role of EMA is not clearly defined in this document with regard to registry of PASS, especially when it is conducted voluntarily by marketing authorisation holders. Concerning safety legislation, to our opinion, the term "encouraged" (lines 532, 536 and 540, but also in lines 176, 193, 315, 324, 369, 493, 498, 507) is too vague and doubtful. Proposed change (if any):
325-337, 496-505 and 531-541		Comment: In our opinion, the processes of registration/communication/publication in the document should be clarified in depth. For reasons of transparency, aspects of PASS's communication (especially in what concerns to registration and final results/ final report) should be crystal clear defined regardless if it is done on a voluntary or on a compulsory basis. Proposed change (if any):

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
Celgene Europe Ltd.

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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 guideline would benefit from better delineation of the processes required for voluntary versus imposed PASS. The organization could be streamlined. For example Sections B.4 describes the outline of the process for review of protocols and amendments without providing details of the regulatory process. Section C.4.2 – describes essentially the same thing but includes more detail of the regulatory process (timelines and expectations). Ideally the repetition could be removed.

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		**Comment:** Include definition that the Agency (referred to throughout the text) is the EMA **Proposed change (if any):**
135-136		**Comment:** Please clarify if the intent of this text is to include all drug utilization studies in this definition. How should sponsors interpret the language – "to assess patterns of drug utilization and use of medicinal product that may have an impact on its safety (e.g. co-medication, mediation errors)? Are there any types of drug utilization studies that would not meet this definition? **Proposed change (if any):**
190-191		**Comment:** Clarify that the "contact person for pharmacovigilance at the national level" – is the sponsor representative – current text is unclear. **Proposed change (if any):**
194		**Comment:** Please provide clarity on (or even better a link to) where the EMA registry is (or will be) located.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 also provide information on the process and requirements of entry of the protocols onto the registry. **Proposed change (if any):**
208		**Comment:** Please clarify what should be included here if the MAH are not acting as the sponsor of the PASS in question **Proposed change (if any):**
229		**Comment:** Please clarify how specific the details of the milestones need to be? **Proposed change (if any):**
277		**Comment:** Please clarify if quality control refers to what is included in the protocol or with the patient details not included in the protocol? **Proposed change (if any):**
294		**Comment:** Please clarify how specific the details of the milestones need to be? **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')*
498-499		**Comment:** Can it be clarified if publication of data as a manuscript is a requirement? **Proposed change (if any):**
506-509		**Comment:** Can it be clarified if submission of any manuscripts of study results to National CA or to the EMA is a requirement or is referenced in the legislation **Proposed change (if any):**
531		**Comment:** Details of links or location of the registry for studies should be included. **Proposed change (if any):**
531		**Comment:** Details of links or location of the registry for studies should be included. **Proposed change (if any):**
542-545		**Comment:** Does this section include EnCEPP non-interventional study registries?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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):
674		**Comment:** Please clarify the process if a letter of objection for a study amendment is received from PRAC. How can sponsors move the process forward? **Proposed change (if any):**
682-686		**Comment:** This paragraph makes no sense in this context. Please clarify what kind of waiver the MAH should be applying for (is unclear what this paragraph refers to) **Proposed change (if any):**

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
Chugai Pharma UK Ltd

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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 nfo@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')*
VIII.B.4.1. :Format and content of the study protocol :Final report of study results		Companies need to describe the milestone in RMP. If the delay of the final report is due to the delay of enrolment to the study, does an amendment of the RMP have to be submitted?
VIII.B.6. :Publication of study results by investigators :		What kind of studies by investigators need to be collected by MAH? Could you provided further details? Do these studies exclude those not supported by companies?
VIII.B.6.1. :Submission of published study results to competent authorities:		Submission of published study results to competent authorities, what is the definition of date of "acceptance" of the publication

Please add more rows if needed.

18.04.2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
CIS bio international

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 193-194		Comment: What are the objectives of this e-register of PASS? What kind of information is especially expected? Are the MAH only “encouraged” to make the study protocol publicly available in the register or should each PASS be register by the MAH? (see also VIII.B.9. lines 532, 540) Would it be possible to add the website link of this e-register? Proposed change (if any):	
Line 354		Comment: would the timing of the progress reports be defined by the relevant competent authorities or would it be agreed with the MAH and the relevant competent authorities? Lines 358-359: Will the expected data (content of the progress report) be specified in advance by the relevant competent authorities? Proposed change (if any):	
Lines 566-575		Comment: May be the sentence “the PRAC will adopt a recommendation to….” can be confusing Proposed change (if any): “the PRAC will provide a recommendation to….”	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 578, 582, 632		Sometimes it is unclear whether it concerns a competent authority of the Member States, where PASS are supervised and assessed by the PRAC (multiple country = PRAC) or a national competent authority, in which national oversight procedures apply (single country = MS)?	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

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

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1. General comments

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

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')*
66-67		Comment: The sentence: "In this context interviews, questionnaires and blood samples may be performed as part of normal clinical practice" is difficult to interpret. It should be clear that "No additional diagnostic or monitoring procedures shall be applied to the patients" in a non-interventional trial as stated in article 2 (c) of directive 2001/20/EC. The same sentence "In this context it is considered important to clarify that interviews, questionnaires and blood samples may be considered as normal clinical practice" in Volume 9A has lead to different interpretation among Member states on the allowance of additional blood samples and questionnaires in non-interventional PASS studies. Proposed change (if any):
74-76		Comment: Proposed change (if any):
174-179 313-316		Comment: Marketing Authorisation holders are encouraged to transmit voluntarily initiated PASS study protocols to national competent authorities prior to initiation. This is outside the scope of directive 2010/84/EU. The final study report will be submitted to the authorities after finalisation of the study and these data are considered to be sufficient. Proposed change (if any): Remove submission of voluntary PASS from guideline.
182-184		Comment: It should be added that PASS initiated pursuant to an obligation needs a written endorsement from NCA or PRAC, as appropriate, before the study is commenced. In accordance with line 658-660. Proposed change (if any): The PASS may commence only when a written endorsement from the national competent authority or the PRAC, as appropriate, has been issued, cf. DIR Art 107n (3).
292-293		Comment: Certain studies where expedited reporting is not required cannot be identified in Module VI. Please

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
341-342		specify where to find the description of certain studies in Module VI or repeat the information in this module. Proposed change (if any):
317-321		Comment: It is not identified where amendments to the protocol shall be submitted – It should be clear that it is the same authority which has issued the written endorsement of the initial protocol. It should be stated that the MAH has to obtain endorsement from NCA or PRAC as stated in 666-673. Proposed change (if any): Please clarify where to submit amendments.
334-336		Comment: Please emphasise the wording in accordance to article 107m, paragraph 7, 3rd subparagraph: "The obligation laid down in the second subparagraph is without prejudice to the information on the results of studies that the marketing authorisation holder shall make available by means of the periodic safety update reports as laid down in Article 107b."
367-370		Submission of the final study report to NCA is obligatory for voluntary PASS according to article 107m, paragraph 6 of directive 2010/84/EU. "The marketing authorisation holder shall send the final report to the competent authorities of the member states in which the study was conducted within 12 months of the end of data collection". Proposed change (if any): The word "encouraged" should be changed to "shall" and a reference to article 107m (6) should be inserted.
621		Comment: MAH needs to ensure that the study is not a clinical trial. The distinction between clinical trials (interventional studies) and non-interventional studies is not harmonized in Europe. To avoid different decisions in Europe on PASS studies, it is suggested that the Commission publish a guideline on the distinction between the two types of studies. Proposed change (if any):
659-664		It follows from article 107n paragraph 3, second subparagraph, that "Where a letter of endorsement as referred to in paragraph 2(a) has been issued, the marketing authorisation holder shall forward the protocol to the competent authorities of the Member states in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 replace the word “should” with “shall” in the sentence beginning with “in cases where”. The following sentence should be rephrased in accordance to the abovementioned quotation from article 107n, paragraph 3.

Please add more rows if needed.

17 April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	The Drug Commission of the German Medical Association (DCGMA) thanks for having given the opportunity to comment on the Guideline on good pharmacovigilance practice. The DCGMA is taking the opportunity to make some general comments to 'Module VIII – Post authorisation safety studies' followed by detailed proposed changes of the text and will also propose changes to the Module V and Module VI. First of all, it is greeted that specific rules have been set up for the post-authorisation safety studies. Having said this, we nevertheless have to criticise that final study reports (VIII.B.5.3.2.) of PASS voluntary initiated by the marketing authorisation holder are differently handled compared to PASS initiated by the marketing authorisation holder pursuant to an obligation imposed in accordance with Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC. We are of the opinion that at least the abstract must be made public and be available in an English translation to ensure that the medical professionals have access to this very important information related to patient safety and necessary to perform an appropriate risk-benefit analysis before prescribing a drug.

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 369		Comment: This information must be available for public information. Proposed change (Line 369): Change "…is also encouraged to transmit the final study report to the national competent authority…" to "…is also **requested** to transmit the final study report to the national competent authority…"
Line 371		Comment: This information must be available for public information. Proposed change (Lines 371 – 372): Please add after the last sentence: "The study report should include a public abstract and the authorisation holder should ensure that an English translation of the abstract is submitted."
Line 499		Comment (Line 499): We are of the opinion that it is indispensable that scientist can independently prepare publications from the work they have performed. Proposed change: Please change "It is recommended that this strategy allows…" to "**It is indispensable** that this strategy allows…".
Line 532		Comment: From our point of view this information must be available. Proposed change (Line 532): Please change "The marketing authorisation holder is encouraged to have information on the study…" to "The marketing authorisation holder **should** have information on the study…".

Please add more rows if needed.

<18 April 2012>

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Overall, this draft module is comprehensive and provides general guidance on the requirements for non-interventional PASS, protocol oversight, and transparency. This guidance is very helpful. 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.
	In common with other GVP modules, this module provides clarification as to the meaning of the words “shall” and “should” (lines 93-94). However, unlike other modules, this module makes several uses of the words “recommend” and, in particular, “encourage”, without clarifying what either means. Do these represent situations where the expectation is that the MAH considers applying the provisions within this module to the situation concerned, or do they represent situations where the MAH would be expected to actually conform with the provisions within the module? This is important as MAHs could be subject to inspection against these new standards from July 2012 onwards, and inspectors must be clear as to what the expectations are in this regard.
	We suggest that this module provide flexibility for certain required components of a study protocol (such as a listing of all investigators and institutions, amendments and updates, data management, data analysis plan, quality control, and feasibility assessment) and study report (such as a listing of all investigators and institutions, amendments and updates, and quality control) to be described at high level in the study protocol and study report and allows detailed information to be documented in stand-alone documents or appendices. This can avoid unnecessary protocol amendments.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
46		It would be helpful to clarify that this refers to EU competent authority, to avoid any potential misunderstanding. Proposed change: ....imposed by an EU competent authority....
67-68		The definition of non interventional studies is helpful, however the statement 'in this context interviews, questionnaires and blood samples may be performed as part of normal clinical practice' continues to generate much debate as to what interventions tip a protocol into interventional. Proposed change: add as sentence from the ISPE non interventional study guidance as further clarification after 'as part of normal clinical practice. *A patient is at no medical risk from being part of an observational study since the treatment and follow-up received by the patient are not changed in the slightest by the study design itself.*
106-107		It is not clear from this sentence if non-EU post-authorisation studies with safety objectives as requested by non-EU authorities are in scope. The sentence should be more explicit as regards what is and is not in scope. Proposed change: ...and conducted outside the EU, either at the request of an EU competent authority, or which form part of the EU RMP.
110-112		Regarding the definition of the start of data collection in secondary data studies, the date of the start of date extraction may not be straightforward. For instance, data may be extracted during protocol development to inform sample size calculations. Proposed change:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Revise to read (line 111): "Start of data collection: the date from which information on the first study patient is first recorded in the study dataset, or, in case of secondary use of data, the date on which the data extraction starts for the purposes of the primary analysis [IM Annex IV.1(2)]."
113		The phrase "...is first completely available." needs further explanation as data may be available and analyzed but not yet validated through chart review. Proposed change: ....is validated and then completely available.
124-125		Comment: The amended Directive includes in the PASS definition a new category of studies not included before, i.e. those with the aim of "confirming the safety profile of the medicinal product". Many post-authorisation studies, primarily aimed at studying treatment effectiveness, quality of life, etc. include confirmation of the safety profile as secondary or tertiary objectives, so the new definition could dramatically increase the number of studies qualifying as PASS, many of which would not provide relevant safety information. Proposed change (if any): The sentence *"Objectives of a non-interventional PASS (and, more generally of any PASS, whether interventional or non-interventional PASS) may include:"* should be replaced with *"A post-authorisation study (whether interventional or non interventional) should be classified as a PASS when its primary objectives include any of the following:"*
126-127		Many MAHs utilise observational data as part of their routine signal detection activities; these include identifying potential signals and most frequent adverse events in a large population. We do not consider these as studies but rather as hypothesis-generation activities and as part of the evidence gathering process for evaluation of safety issues. Proposed change: "...occurring in a large population over time); note that use of observational databases

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		(claims or electronic healthcare records) for the purposes of signal detection or signal refinement are not considered as PASS;
175-178		This indicates that the MAH will be 'encouraged' to transmit study protocols to the relevant competent authorities for PASS voluntarily initiated by the MAH. It is unclear whether this represents an expectation or whether the guidance is such that this action should be considered by the MAH. Proposed change: For PASS voluntarily initiated by the marketing authorisation holder, the marketing authorisation holder should consider transmitting the study protocol prior to the start of data collection to the National Competent authority of the Member States where the product is authorized and/or to the Agency for PASS concerning products authorised pursuant to Regulation (EC) No 726/2004, as appropriate. The MAH may be required...
181 and 549		Use of the word 'obligation' may be misinterpreted to pertain to specific obligations only. Use of the term 'condition or obligation' in line with the articles referred to would be clearer. Proposed change: "...condition or obligation..."
181-186		The sentence *"For PASS initiated by the marketing authorisation holder pursuant to an obligation imposed in accordance with Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC, see VIII.C.4.2.. Prior to the start of data collection, the marketing authorisation holder must ensure that information on the study, including the study protocol, is notified to the Agency or the national competent authority, as applicable, and that the Member State in which the study is conducted is informed"* is split (dot and capital letter for "Prior") and does not specify to which competent authority the protocol must be sent. In addition, the wording "is notified" does not reflect that the draft protocol will be submitted for review/ endorsement.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): The above sentence should be amended as follows: *"For PASS initiated by the marketing authorisation holder pursuant to an obligation imposed in accordance with Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC, see VIII.C.4.2., prior to the start of data collection, the marketing authorisation holder must ensure that ~~information on the study, including~~ the draft study protocol, is ~~notified~~ submitted for review to the Agency or the national competent authority which requested the study, as applicable, and that the Member States in which the study is conducted are informed".*
188-192		This indicates that the EU QPPV should sign off the study protocol. Other mechanisms than a wet-ink signature should be allowed for. Likewise, the text should allow for local contact persons to have access to the protocol via electronic means. Proposal: amend to "In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) or their delegate (see Module I) should be involved in the review and approval of study protocols. Where applicable, the contact person for pharmacovigilance at national level should be informed of any study conducted in that Member State are made aware of and have access to the protocol."
188-192		This indicates that the EU QPPV should sign off the study protocol. Other mechanisms than a wet-ink signature should be allowed for. Likewise, the text should allow for local contact persons to have access to the protocol via electronic means. Proposal: amend to "In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) or their delegate (see Module I) should be involved in the review and approval of study protocols. Where applicable, the contact person for pharmacovigilance at national level should be informed of any study conducted in that Member State are made aware of and have access to the protocol."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
193-194		This indicates that the MAH will be 'encouraged' to make the study protocol publicly available in the Agency PASS register, presumably including those studies voluntarily initiated by the MAH. It is unclear whether this represents an expectation or whether the guidance is such that this action should be considered by the MAH. Proposed change: The marketing authorisation holder should consider making the study protocol publicly available in the register of non-interventional post-authorisation safety studies maintained by the Agency.....
210-211		For prospective, non-interventional studies which often involve large numbers of sites, it would be a significant task to establish all sites up front and then amend the protocol as and when there are changes to site participation. This could cause significant delay in start of study conduct. The approximate number of sites aimed for and the type of institutions/clinics or institution mix and representative selection of sites will be described in the protocol section 9.2. In contrast to clinical trials, everyone qualified to prescribe a medicinal product should also qualify to participate in a non-interventional study – another good reason not to require all investigators to be listed in the protocol. Proposed change: **Responsible parties:** names, titles, qualifications, addresses and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator and a coordinating investigator for each country in which the study is to be performed.
269-270, 271-276, 277-282, 301-306		For some studies, the detailed Data Management, Data Analysis, Quality Control procedures and Feasibility Study can be too voluminous to be included in the body of the study protocol. Proposed change: Revise the guideline to indicate that it is acceptable to include only high-level summaries of the Data Management Plan, the Data Analysis Plan, and Quality Control Plan and Feasibility Study in the study protocol. The guideline should state that the detailed Data Management Plan, Data Analysis Plan and Quality Control

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Plan can be maintained as stand-alone documents apart from study protocol. The revised guideline also should allow for the modification of these stand-alone documents outside of the protocol change control procedures that are outlined in Section VIII.B.4.2 (Change control of the study protocol). Line 204: "*The study protocol should follow the following format <u>when appropriate and practical</u>*:" And insert after line 306, as a new paragraph: *<u>"When appropriate, e.g., for voluminous documents, the detailed Data Management Plan, Data Analysis Plan and Quality Control Plan can be maintained as stand-alone documents apart from the study protocol. These stand-alone documents may be maintained outside of the protocol change control procedures that are outlined in Section VIII.B.4.2 (Change control of the study protocol), but summary information must be accurately represented in the study protocol."</u>*
298-299		This indicates that the Annexes should include the ENCePP Checklist for Study Protocols signed by the principal investigator. While this may be a reasonable expectation for PASS studies required by the EU competent authorities, does this also apply to PASS voluntarily initiated by the MAH? If the latter, what is the legal basis for such an expectation? Proposed change: <u>The MAH should consider utilising the ENCePP Checklist for Study Protocols and include it in the study protocol annexes accordingly.</u>
309-310 and 321		The guidance refers to "substantial changes" and "substantial amendments", but "substantial" is not defined. The same principles as applied to substantial amendments to clinical trials should apply (EudraLex Volume 10, Chapter 1). Proposed change:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Add "In this context, amendments to the protocol are regarded as substantial where they are likely to have a significant impact on: — the safety or physical or mental integrity of the clinical trial participants, or — the scientific value of the trial."
315		This indicates that the MAH will be 'encouraged' to transmit updated study protocols to the relevant competent authorities for PASS voluntarily initiated by the MAH. It is unclear whether this represents an expectation or whether the guidance is such that this action should be considered by the MAH. Proposed change: For PASS voluntarily initiated by the marketing authorisation holder, the marketing authorisation holder should consider transmitting the updated protocol....
321		It would be helpful to indicate to whom substantial amendments should be submitted and also that substantial amendments require review/endorsement. Proposed change: "..and any substantial amendments to the protocol shall be submitted to the national competent authority that requested the study or to the PRAC, for review before their implementation. Where applicable, the marketing authorisation holder shall inform Member States in which the study is conducted."
323		This indicates that the MAH will be 'encouraged' to have the updated study protocol entered in the Agency PASS register, presumably including those studies voluntarily initiated by the MAH. It is unclear whether this represents an expectation or whether the guidance is such that this action should be considered by the MAH. Proposed change: The marketing authorisation holder should consider entering the updated study protocols in the register of non-interventional post-authorisation safety studies maintained by the Agency.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
330		"Any new information that might influence the evaluation of the risk-benefit shall immediately be communicated" requires further explanation as, for database studies, data are frequently provided to the MAH at preset dates, which may be several months after the event. Proposed change: Any new information that the MAH becomes aware of that might influence…..
364-367		The sentence "The study report should be submitted to the competent authority(ies) as soon as possible after finalisation and within 12 months of the end of data collection" does not make clear whether this refers to the authorities of the countries where the product is authorised or where the study is being conducted. This is specified in the next sentence, literally copied from the Directive, using the term "shall" instead of "should", which may create confusion, considering the different requirements for voluntary PASS vs. imposed PASS described in the following paragraphs. Proposed change: The 2 sentences in 364-367 should be integrated into a single sentence, as follows: "The study report of any PASS (whether initiated voluntarily or imposed by Health Authorities) shall be submitted to the competent authority(ies) of the Member States in which the study was conducted as soon as possible after finalisation and within 12 months of the end of data collection".
364-365		Suggest further clarification of 'end of data collection' as some studies require validation of health outcomes of interest data for example. Proposed change: .... and within 12 months of the end of data collection and, if necessary, data validation.
369		This indicates that the MAH will be 'encouraged' to transmit the final study report to the relevant competent authorities for PASS voluntarily initiated by the MAH. It is unclear whether this represents an expectation or whether the guidance is such that this action should be considered by the MAH.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change: For PASS voluntarily initiated by the marketing authorisation holder, the marketing authorisation holder <u>should consider transmitting</u> the final study report....
372-375		The sentence *"For PASS initiated by the marketing authorisation holder pursuant to an obligation imposed in accordance with Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC, see VIII.C.4.2. Unless a waiver has been granted, the marketing authorisation holder shall, within 12 months of the end of data collection, submit the final study report, including a public abstract, to the Agency and the national competent authority, as applicable"* is unintentionally split (dot and capital letter for "Unless"), is not fully in line with the Directive ("and" versus "or") and does not specify the competent authority it refers to. Proposed change :The above sentence should be amended as follows: "For PASS initiated by the marketing authorisation holder pursuant to an obligation imposed in accordance with Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC, see VIII.C.4.2., <u>unless</u> a waiver has been granted, the marketing authorisation holder shall, within 12 months of the end of data collection, submit the final study report, including a public abstract**,** to the Agency <u>or the national competent authority having requested the study</u>, as applicable".
376		It is unclear what is mean by a 'public abstract'. Proposed change: Please provide clarification whether it is considered public if the abstract is posted on the Agency's register of PASS, or whether it has to be a publication in a scientific journal.
498		This indicates that the MAH will be 'encouraged' to agree in advance a publication strategy with the principal investigator, presumably including those studies voluntarily initiated by the MAH. It is unclear whether this represents an expectation or whether the guidance is such that this action should be considered by the MAH. Proposed change: ....the marketing authorisation <u>should consider agreeing</u> in advance a publication strategy

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		with the principal investigator.
507		This indicates that the MAH will be 'encouraged' to transmit the final manuscript, presumably this includes PASS voluntarily initiated by the MAH. It is unclear whether this represents an expectation or whether the guidance is such that this action should be considered by the MAH. Proposed change: The marketing authorisation holder should consider transmitting the final manuscript....
532-541		This indicates that the MAH will be 'encouraged' to undertake various 'study registration activities', presumably including those studies voluntarily initiated by the MAH. It is unclear whether this represents an expectation or whether the guidance is such that this action should be considered by the MAH. Proposed change: The marketing authorisation holder should consider having information on the study, including the study protocol, entered prior to the start of data collection into the electronic register of non-interventional post-authorisation safety studies maintained by the Agency. This information should include an English translation of the title of the study and of the abstract of the study protocol. In case of substantial amendments to the study protocol, the marketing authorisation holder should consider having the revised study protocol entered into the electronic study register (see also VIII.B.4. for cases where publication of the protocol could threaten the validity of the study or the protection of intellectual rights). At the end of the study, the marketing authorisation holder should consider having the final study report entered into the electronic study register, including an English translation of the abstract.
551		Typo: VIII.C.7 doesn't exist –should refer to VIII.C.5 Proposed change: ...VIII.C.4 to VIII.C.5...
583		This indicates that the relevant competent authority should 'encourage' concerned MAHs to conduct a joint

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		PASS. It is unclear whether this represents an expectation or whether the guidance is such that this action should be considered by the MAH, most probably the former is intended. Proposed change: If safety concerns apply to more than one medicinal product, the national competent authority or the Agency shall, following consultation with the PRAC, recommend that the marketing authorisation holders concerned should conduct a joint PASS.
603		The variation classification to be used for inclusion of a new PASS obligation should be clarified. The classification should be consistent with existing variation classifications for implementation of product information changes requested by the competent authority, as defined in section C.1 of the Commission Guideline on the categories of variations (2010/C 17/01). The required supporting documentation should be minimal and the fee should be nominal, given that the assessment has already taken place under a separate procedure.
608-609		This states that PASS imposed as a condition to the MA will be described in the RMP. However, draft GVP module V (lines 1009 – 1015) indicate that all post-authorisation safety studies should be included in the RMP. It should be ensured that the two modules are consistent with each other.
609		Results may not be available for the next PSUR, so some flexibility should be permitted. Proposed change: "The results should be provided in the next appropriate PSUR..."
640		To ensure consistency, the same rapporteur should be utilised for assessment of PSURs and RMP for the product addressed by the PASS. Proposed change: In case the PRAC is involved in the oversight of the study, the PRAC will nominate a PRAC rapporteur responsible for the supervision of the PASS, this rapporteur when possible will be the same as 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')*
		responsible for the assessment of associated PSURs and RMPs for the product concerned.
664		The text implies that a competent authority may have to acknowledge receipt of the PRAC endorsement before the PASS may commence. This is not consistent with Article 107n(3), which states that the study may commence after the MAH has forwarded the protocol to the participating Member State. No further competent authority confirmation or approval is required following PRAC endorsement of a non-interventional PASS, in order to commence the study. Proposed change: The study may start only on receipt of the letter of endorsement by the PRAC and only after the MAH has forwarded to the relevant national competent authority(ies) ~~have received~~ a copy of the PRAC endorsed protocol [DIR Art 107n(3)].
675-676		Comment: The required report submission to PRAC is not fully in line with lines 372-375 requiring submission to the Agency. Proposed change (if any): The above inconsistency should be resolved.
694-698		Comment: The request to submit any necessary variation with the final study report within 12 months of the end of data collection may be very difficult to implement since, once the study report is available, some time is needed to prepare the variation package. In addition, the PASS may trigger a labelling change of minor relevance (such as the addition of one non-serious ADR) and it may be inappropriate in terms of economy and practicality to immediately file a variation due to this one change alone instead of combining potential new risks arising from other sources. Either a risk based approach should therefore be introduced or a time frame of at least 3 months, after completion of the study report, should be allowed to submit the necessary variation. 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')*
		"At time of submission of the final study report, the marketing authorisation holder should evaluate whether the results have an impact on the marketing authorisation and shall, if necessary, commit to submit to the national competent authorities or the Agency an application to vary the marketing authorisation within 3 months....." Or, for a risk based approach: "At time of submission of the final study report, the marketing authorisation holder should evaluate whether the results have an impact on the marketing authorisation and shall, if necessary, commit to submit to the national competent authorities or the Agency an application to vary the marketing authorisation [DIR Art 107p(2)]. In such case, depending on the importance of the risk for public health and the benefit risk profile of the product, a reasonable timeline for submission of the variation to the national competent authority or the Agency should be chosen. In the event of an important risk, submission together with the final study report within 12 months of the end of data collection should be aimed for. Any minor findings which lead to an addition of a new adverse reaction may be introduced by variation within 12 month after submission of the final report unless either the QPPV or the NCA request differently based on the assessment of the finding."
798-800		Active surveillance programs should be included. Proposed change: Revise to read: "*There are a number of observational study designs that are useful in validating signals from spontaneous reports, active surveillance programs or case series*".

17 April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

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 considers that a clear definition has to be made on PASS and a clear difference should be made between PASS and PAES. Concerning PASS, the primary endpoint should be a safety outcome.
	The EGA would like to stress that joint forces are a good idea might be needed to perform PASS, but is concerned about the division of the work between the companies. Who will be responsible for this and who will be organizing this? Will this be the responsibility of the PRAC? A few difficulties are identified by the EGA pharmacovigilance and regulatory working group: - Who will be the owner of the PASS data? - Who will pay for his joint studies? - Who will handle this in his PSMF? - Who will be responsible for making the protocols? An answer to these questions should be defined together with the publication of the GVP module.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 97-101		Comment: the scope of the guidance apply to non-interventional PASS, which are initiated, managed or financed by the MAH ... Proposed change (if any): PASS that are not initiated and managed by the MAH but are partially sponsored by the MAH or more MAHs (eg. material costs without compensation for the investigators) should be exempted from the requirements as the MAH does not have influence on its design and managements.
Lines 105-106		Comment: Studies outside the EU are usually conducted in-line with national legislation, which may be contradictory to this guidance. Proposed change (if any): The use of guidance outside of the EU should only be recommended to MAH; the word should is too binding.
Lines 120-122		Comment: The EGA agrees that such studies shall not be performed where the act of conducting the study promotes the use of a medicinal product. However by some authorities the involvement of marketing personnel itself (e.g. for monitoring) may be understood as a promotional act even if the staff only monitor compliance according to protocol. Marketing personnel are frequently the only available resources able to provide services needed on the local sites at reasonable costs. Proposed change (if any): It should be highlighted that involvement of marketing personnel should not be regarded as promoting the use of products if the study is conducted according to approved protocol.
Lines 167-168		Comment: Payments to healthcare professionals shall be restricted to compensation for time and expenses incurred.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): The EGA suggests that national authorities agree with national medical chambers on recommended payments based on time unit and investigator's expertise and expenses incurred so that the payments will be acceptable for investigators.
Lines 175-180		Comment: The MAH is encouraged/obliged to submit study protocol to NCAs in the MS where the **product is authorised** and to the Agency .... to NCAs of MS where the **study is conducted**. Proposed change (if any): the submission schedule is confusing. Non-interventional safety study may only be conducted in MSs where the product is authorised and on the market. We suggest that protocol should be submitted only to NCA in MSs where the study is conducted.
Lines 187-191		Comment: The QPPV should be involved in the review and sign –off of study protocols. It is not clear as this duty can be delegated. Proposed change (if any): It should be highlighted that delegation of the review and sign-off of study protocols can be delegated.
Line 227		Comment: the reference to VIII.B.1. is erroneous Proposed change (if any): – it should be corrected to VIII.B.2
Lines 327-334		Comment: Communication of information that may change the benefit/risk balance is not in accordance with Module VIII. As such information represent a safety signal it should be communicated he same way as other signals (as described in Module VIII).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): The EGA suggests sending such information to the lead/co-lead MS and not to every MS where the product is conducted.
Lines 478-492		Comment: The abstract is too detailed. Discussion is a whole section and falls outside the scope of an abstract.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18-April-2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

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**.**

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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: The Risk management systems Module V states generally that drug utilisation studies conducted for Health Technology Assessment purposes are to be treated as post-authorisation safety studies and included in risk management plans (see comment above). This statement is not consistent with the definition of post-authorisation safety studies contained in the legislation and repeated in this Module.
	Recommendation regarding Comment 1: The Module should advise that drug utilisation studies conducted for Health Technology Assessment purposes should become part of a risk management plan only if they meet the definition of post-authorisation safety studies.
	Comment 2: There is a lack of clarity as to the distinction between voluntary post-authorisation safety studies and imposed post-authorisation safety studies in the Module, in particular the Module does not address the position at the point of approval when studies are negotiated between Marketing Authorisation Holders and the Agency/Competent Authority.
	Recommendation regarding Comment 2: Improve the description of what constitutes a post-authorisation safety study “imposed” by the Agency/a Competent Authority.
	Comment 3: The Module refers to the involvement of the QPPV in sign off of post-authorisation safety study protocols. It is not clear what would constitute acceptable “involvement” or whether the QPPV would be expected to approve all post-authorisation safety studies. It would not be practical to expect the QPPV’s personal signature of post-authorisation safety study protocols.

Stakeholder number *(To be completed by the Agency)*	General comment
	Recommendation regarding Comment 3: Clarification as to exactly what would be acceptable by way of QPPV “involvement” is needed. In line with the accepted approach to the performance of other QPPV responsibilities by regulatory authorities, this should not require individual QPPV signature of every protocol.

April 4, 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
Dr. Ernst Weidmann, Auf der Forst 24, 45219 Essen, Germany

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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 important question to be answered by PASS is the safety in routine clinical use. This includes the documentation of compliance with the SPC and the documentation of potential off-label use and its impact on the safety profile. Uncertainties have developed concerning the non-interventional status of these studies in this aspect within ECs, competent authorities and MAH. The definitions laid out in the ENCePP CONSIDERATIONS ON THE DEFINITION OF NON-INTERVENTIONAL TRIALS UNDER THE CURRENT LEGISLATIVE FRAMEWORK (“CLINICAL TRIALS DIRECTIVE” 2001/20/EC) answer these issues and therefore should be referred to, to avoid these ambiguities. The current wording of the GPV Module VIII PASS does not fully meet this challenge and needs improvement.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
135		Comment: The text does not refer to the fact that drug utilisation studies are always non interventional and does not refer to the documentation of off-label use/compliance with the SPC as a major goal. Proposed change (if any): Add off-label use to the examples in parenthesis Use the definition of the ENCePP CONSIDERATIONS ON THE DEFINITION OF NON-INTERVENTIONAL TRIALS UNDER THE CURRENT LEGISLATIVE FRAMEWORK (“CLINICAL TRIALS DIRECTIVE” 2001/20/EC) pg 4 last paragraph and page-5 first paragraph.
144-16		Comment: In the references made to ENCePP documents the relevant ENCePP guidance for non-interventional trials is missing Proposed change (if any): Add the relevant guidance : ENCePP CONSIDERATIONS ON THE DEFINITION OF NON-INTERVENTIONAL TRIALS UNDER THE CURRENT LEGISLATIVE FRAMEWORK (“CLINICAL TRIALS DIRECTIVE” 2001/20/EC)

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18. April 2012

Submission of comments on 'GVP Module VIII – Post-authorization safety studies' (EMA/813938/2011)

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*).*

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
	Overall, the document appears consistent with the regulation/directive and very helpful for interpretation. The guideline would, however, benefit from better description of the processes required for voluntary versus imposed PASS. The organization could be streamlined. For example Sections B.4 describes the outline of the process for review of protocols and amendments without providing details of the regulatory process. Section C.4.2 – describes essentially the same thing but includes more detail of the regulatory process (timelines and expectations). Ideally the repetition could be removed. Further improvements could be achieved through • using more examples • In section dedicated to non-interventional design, such as VIII.B, being more strict/repetitive in using the term "non-interventional studies" instead of "studies" • Including an index of relevant terms indicating the pages where they are addressed
	General comment on Examination of off-label use within post authorization safety studies (as a part of the investigation of the use of a medicinal product in clinical practice). It is recognized that a post authorization study could be initiated as a clinical trial according to Directive 2001/20/EC but an investigation of the use of a medicinal product in clinical practice should be made without any influence of the prescribing physician meaning a non interventional study. According to Vol 9A a PASS was defined as a non-interventional trial for the investigation of the use of a medicinal product in

Stakeholder number *(To be completed by the Agency)*	General comment
	clinical practice without influencing the prescribing and without additional investigations other than those foreseen in the product information. These studies shall be conducted amongst other objectives "…if there is concern regarding the use of the medicinal product (e.g. to quantify the off-label use)…." This is also in line with the ENCEPP Considerations on the definition of Non-Interventional Trials under the current legislative framework (clinical trials directive): "Similarly, the following prospective studies should never be considered as falling within the scope of Directive 2001/20/EC: Studies which evaluate patterns of the usage of medicines, including potential off-label use or measuring the effectiveness of risk management measures in current practice, such as collection of data on drug utilization and occurrence of health outcomes." The qualitative and quantitative compliance in clinical practice with standards given in the SmPC can only be documented in an observational study, where the use of the product is not determined by an interventional protocol. Since the off-label use is assessed in retrospect by the analysis of the indication for use (normally in the case record form) there is no risk to promote the off-label use within in a post-authorization safety study. In some European countries like Germany the use of a product outside the approved indication is not permitted in non interventional studies. According to the German Medicinal Products Act (AMG) a non-interventional study is defined in the following way: A non-interventional trial is a study, in the context of which findings resulting from persons' treatment with medicinal products are analyzed using epidemiological methods; the treatment, including the diagnosis and monitoring, shall not follow a predetermined

Stakeholder number *(To be completed by the Agency)*	General comment
	trial protocol but shall result exclusively from current medical practice; in so far as a medicinal product requiring a marketing authorization or a medicinal product requiring an authorization pursuant to Section 21a sub-section 1 is concerned, this shall be conducted, moreover, according to the specifications regarding its use contained in the marketing authorization or authorization." So the evaluation of an off-label use within in a post-authorization safety study, which is/was/will agreed with the EMA is not permitted at the moment.

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')*
after Line 65		**Comment:** Add an advice concerning the decision for using on non-interventional study as explained in the question and answer document. **Proposed change (if any):** Please add the following sentence after line 65: “These trials are typically of a lower risk than interventional clinical trials. This shall ensure that medical activities are normal clinical practice and as such part of the general medical surveillance of a patient.”
Line 66 - 67		**Comment:** Example(s) what would constitute a violation of the non-interventional context would be helpful. Particularly the relevance of drawing blood samples in this context might be difficult to assess?
After Line 67		**Comment**: Add an advice how to proceed concerning the evaluation of off-label use. **Proposed change (if any):** Please add the following sentence after line 67: In case of evaluating the possible off-label use this shall be requested via the case report form field indication
Line 106		**Comment**: The legal basis of this GVP Module for studies developed and conducted outside the EU is not clear

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): The following aspect should be added: …outside the EU, <u>which have been requested by the Agency or competent authority</u> These guidance and requirements should also be considered by marketing authorization holders for studies developed and conducted outside the EU, <u>which have been requested by the Agency or competent authority</u>.
Line 108		**Comment:** Include definition that the Agency (referred to throughout the text) is the EMA
Line 135-136		**Comment:** Please clarify if the intent of this text is to include all drug utilization studies in this definition. How should sponsors interpret the language – "to assess patterns of drug utilization and use of medicinal product that may have an impact on its safety (e.g. co-medication, mediation errors)? Are there any types of drug utilization studies that would not meet this definition?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 147 ff		**Comment**: Here the concept of "Investigator Sponsored (but industry "funded" ..) Studies" is extended to the non-interventional context? This should be made clear and the requirements for NIS should not exceed those as defined for interventional studies. Also, would the QPPV resume responsibility for ADR reporting from these studies?
Line 174 - 186		**Comment:** In this section it is stated that for PASS voluntarily initiated by the marketing authorization holder, the marketing authorization holder is encouraged to transmit the study protocol prior to the start of data collection to the national competent authority of the Member States where the product is authorized and to the Agency for PASS concerning products authorized pursuant to Regulation (EC) No 726/2004. The marketing authorization holder may be required by the national competent authority to submit the protocol to the competent authorities of the Member States in which the study is conducted [DIR Art 107m(5)]. On the other hand, for PASS initiated by the marketing authorization holder pursuant to an obligation imposed in accordance with Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC, VIII.C.4.2. applies. Prior to the start of data collection, the marketing authorization holder must ensure that information on the study, including the study protocol, is notified to the Agency or the national competent authority, as applicable, and that the Member State in which the study is conducted is informed.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		That information shall include an English translation of the title and abstract of the study protocol [IM Annex IV.1(4)]. In our opinion it would be more convenient if the core information to be submitted would be the same regardless of whether the PASS has been initiated voluntarily or has been an obligation.
Line 187 ff		**Comment:** The QPPV (e.g. for PASS conducted in Europe) has the responsibility for ADR resulting from NIS and thus rather MUST have a final say how they are conducted, particularly for studies planned voluntarily.
Line 190-191		**Comment:** Clarify that the “contact person for pharmacovigilance at the national level” – is the sponsor representative – current text is unclear.
Line 194		**Comment:** Please provide clarity on (or even better a link to) where the EMA registry is (or will be) located. Please also provide information on the process and requirements of entry of the protocols onto the registry.
Line 208		**Comment:** Please clarify what should be included here if the MAH are not acting as the sponsor of the PASS in question

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 229		**Comment:** Please clarify how specific the details of the milestones need to be?
Line 277		**Comment:** Please clarify if quality control refers to what is included in the protocol or with the patient details not included in the protocol?
Line 294		**Comment:** Please clarify how specific the details of the milestones need to be?
Line 309 - 312		**Comment**: The procedure and the involvement of the Agency and the competent authorities concerning the change of the classification of a non-interventional trial into a clinical trial should be defined in more detail. **Proposed change (if any):** If changes to the protocol lead to the study being considered an interventional clinical trial the Agency or the competent authority should be informed immediately.~~, the study shall subsequently be conducted in accordance with Directive 2001/20/EC and Volume 10 of The Rules Governing Medicinal Products in the European Union.~~
Line 335 ff		**Comment:** Prospective observational design: Would the authorities encourage collecting AE from which suspected ADR shall be identified via investigator assessment or would generally only an ADR documentation expected? An

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		opinion would be appreciated here, including whether this could be handled differently?
Line 385 ff		**Comment**: With large scale prospective observational studies conducted internationally in general practice: Listing (hundreds?) of names of investigators as part of the study report appears inappropriate. Could this be restricted to interventional PASS and for observational NIS the respective specialties of physicians could be listed instead?
After Line 461		**Comment**: add the definition of off-label use **Proposed change (if any):** 10.7 Off-label use
Line 466 ff		**Comment:** Examples in the context of a NIS would be appreciated.
Line 498 - 504		**Comment:** It is recommended that this strategy allows the principal investigator to independently prepare publications based on the study results irrespective of data ownership. In this case, the marketing authorization holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication, while avoiding unjustifiable delays of the publication. Requests for changes to the manuscript should be based on sound scientific reasons. The marketing authorization holder should be allowed to require deletion of confidential information

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		In our opinion some information on authorship or adequate references (rules according to the "Vancouver protocol" / European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)) would be helpful.
Line 506 – 508		**Comment:** The marketing authorization holder is encouraged to transmit the final manuscript of the article to the Agency and the competent authorities of the Member States in which the product is authorized within two weeks after acceptance of the publication. It is not really clear if the document will get published once it was submitted (if so that would be a critical point as "acceptance of a publication" is not always equal with the "publication of the manuscript" itself (potential for a "conflicting interests" which needs clarification). Can it be clarified if publication of data as a manuscript is a requirement?
Line 531		**Comment:** Details of links or location of the registry for studies should be included.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 531		**Comment:** Details of links or location of the registry for studies should be included.
Line 542-545		**Comment:** Does this section include EnCEPP non-interventional study registries?
Line 581 - 595		**Comment:** It is mentioned that if safety concerns apply to more than one medicinal product, the national competent authority or the Agency shall, following consultation with the PRAC, encourage the marketing authorization holders concerned to conduct a joint PASS [DIR Art 22a, REG Art 10a]. Requests to the marketing authorization holders should contain the elements of the study design that support the joint proposal. Upon request from the marketing authorization holders, the national competent authority or the Agency may organize a pre-submission meeting in order to provide suggestions for a joint proposal and facilitate agreement in developing a joint protocol. If a joint protocol is not voluntarily agreed and different proposals are submitted, the national competent authority or Agency may adopt, in consultation with the PRAC, the key elements (for example, the study design and the definition of exposure and outcomes) which each marketing authorization holder should include in the study protocol. These key elements may then be imposed on all the marketing authorization holders, pursuant to Article 22a of Directive 2001/83/EC or Article 10a of Regulation (EC) No 726/2004. The study protocols should be implemented within a timescale laid down by the national competent authority or the Agency in consultation with the PRAC and imposed according to Article 22a of Directive 2001/83/EC or Article 10a of Regulation (EC) No 726/2004. The definition of timelines would be helpful.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 674		**Comment:** Please clarify the process if a letter of objection for a study amendment is received from PRAC. How can sponsors move the process forward?
Line 682-686		**Comment:** This paragraph makes no sense in this context. Please clarify what kind of waiver the MAH should be applying for (is unclear what this paragraph refers to)
Line 729 ff		**Comment:** Listing of presented methodology under two main sections: NON INTERVENTIONAL and INTERVENTIONAL (Clinical Trials) might be supportive. Also replacing trial by "study" might add to consistency.
After Line 901		**Comment**: Add information related to the evaluation of off-label use within drug utilization studies. As also proposed by the ENCEPP Considerations "Drug utilization studies are useful tools in evaluating the patterns of use of a medicinal product, including capturing off-label use and can be conducted with this specific aim." **Proposed change (if any):** DUS may be used to examine the relationship between recommended and actual clinical practice <u>including capturing off-label use</u>.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
European Organisation for Rare Diseases

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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')*
166-167		Comment: When applicable, PASS participants (i.e. the patients) are entitled to receive information about the results of the study they were on, or for which their tissue samples were used. Proposed change: • communication strategy for the scheduled progress and final reports; • Measures taken to inform participants about the study to be conducted, when applicable; • publication strategy of interim and final results, including to the participants (when applicable).
203-306		Comment: even when the PASS is not a clinical trial but a non-investigational study, it is important to inform patients who will participate about the study (in prospective cohort studies, or patient questionnaires/surveys…) Proposed change: a copy of the participant information letter should be part of the study protocol to be submitted to PRAC and/or national authority
295-296		Comment: See above 166-167 Proposed change: 12. plans for disseminating and communication study results including plans for submission of progress reports, final reports and publications, and including participants as target group of the communication plan.
372-378		Comment:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		The possibility to ask for a waiver in case of the reporting delay after study completion may not be respected is mentioned. There will be cases where the requested PASS studies will not be conducted, for practical reasons (lack of patients, lack of healthcare professionals interested to participate etc.) or other reasons. However there are no guidelines on how to discuss with PRAC and/or national authority on the difficulties met by the MAH when requested to conduct a PASS. At the time of Post-Marketing Commitments, the MAH had the possibility to explain the difficulties encountered with the CHMP and in some cases both parties could come to an agreement, to lift the request to conduct additional studies. There are no such provisions in these guidelines, no description on how to obtain a waiver, in case a PASS cannot be initiated or completed, despite efforts to do so.
577-605		Comment: When an emergent safety concern has been brought to the attention of competent authorities by a patients' organisation, and competent authorities then request a post-authorisation safety study, it would be fair to involve the patients' organisation in the design and supervision of the PASS in question, both to recognise the contribution of the patients' organisation, and to ensure best possible follow-up Proposed change: to add When an emergent safety concern has been brought to the attention of competent authorities by a patients' organisation, and competent authorities then request a post-authorisation safety study, it is recommended to involve the patients' organisation in the design and supervision of the PASS in question.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 17th, 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

EVM

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

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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
	EVM is in agreement with general comments of EFPIA
	This guideline should provide more details on the circumstances that a PASS is recommended, encouraged, and/or required to do or not.
	There is a particular need for more guidance on vaccine PASS to discuss about the vaccine PASS designs that are appropriate and important for vaccine research because of the lack of appropriate separate comparison groups, rapid public vaccine campaign, and restricted risk windows for certain outcome of interest following vaccination. Given public health importance and high impact of vaccine safety concern on the population, a specific guideline for vaccine PASS would help to define if the agencies and MAH should speed up a PASS in an epidemic situation, and how.

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 61-66		Comment: A prospective observational study listed as an example in line 64-65 may also be a cohort study. The categorization of the study examples in the two sentences is confusing. Particularly, not all cohort studies are based on database or medical record review. Proposed change: Change the text as follows l. 63: "(e.g. ~~case-control, cross-sectional and~~ *database-based retrospective* cohort studies)" l. 65: "(e.g. prospective observational *cohort* studies)"
Line 106		Comment: The statements "should also be considered by MAH for studies developed and conducted outside the EU" needs clarification. Proposed change: Change text as follows "…should also be ~~considered~~ *followed* by MAH *if the studies outside the EU are included in the dossier submitted to the EMA* ~~for studies developed and conducted outside the EU~~".
Lines 133-134		Comment: The statement "to evaluate risks of a medicinal product **used in authorised indications by patient groups** not studied in the pre-authorisation phase (e.g. pregnant women, elderly patients);" appears to be conflicting in some cases. For instance it is not clear if it could be an authorized indication if the patient group had not been studied in pre-authorization phase. Proposed change: Change text as follows "to evaluate risks of a medicinal product *in patient population* ~~used in authorised indications by patient groups~~ not studied in the pre-authorisation phase (e.g. pregnant women, elderly patients)"
Line 254		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')*
		It is suggested to separate "exposure" from "variables". It is particularly important for a PASS with vaccines given that the exposure may be for primary and / or for booster dose, while the schedule of administration may vary between EU countries (e.g. schedule 3+booster i.e. 2-3-4 Mo of age + booster or schedule 2+1 i.e. 3-5-12 Mo of age) and the safety may be different with the different schedules. The route of administration may be different as well (IM or SC). For other medicinal products the daily dose and the duration of treatment may vary. Proposed change: It is suggested to separate "exposure" from "variables"
Lines 340-343		Comment: Is the reporting of suspected AEs required for database studies?
Line 423		Proposed change: It is suggested to move "bias" paragraph to the "discussion" section.
Lines 559-561 & 600-602		Comments: Regarding (l.559-561) "The request (for PASS) may also recommend key elements of the study (e.g., study design, setting, exposure(s), outcome, population to be addressed" and (l. 600-602) "On the basis of written observations submitted by MAH, the national competent authority, the Agency or EC shall withdraw or confirm the obligation", we hope that the imposed elements of the obligatory PASS will be discussed with MAH prior to formal written request from the Agency. The approach seems to be very prescriptive by the Agency with very little input and feedback about feasibility of the study that MAH may have based on prior experience in specific country or with access to the population database. Proposed change: It should also be specified that communications between the MAH and EMA have to be foreseen prior to written notification when it comes to the design of the study and the feasibility.
Line 616		Comments: To determine if "results of the post-authorisation safety study require a variation to the marketing

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		authorisation…", a quantitative or qualitative benefit risk assessment will probably be needed by including both pre-authorization and post-authorization data. In addition, as an epidemiologic study, the study results may not be conclusive which justify further studies. Proposed change: It is suggested to discuss about the need of the B/R assessment and in what specific situation, a RMP update would be needed.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18/04/12

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
Faculty of Pharmaceutical Medicine

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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')*
Page 3 – line 54		Comment: also include medicines that are non-prescription Proposed change (if any):
Page 11 – line 364		Comment: swap the order of the two sentences in this paragraph – it would read more clearly. Proposed change (if any): The marketing authorisation holder shall submit the final study report to competent authorities of the Member States in which the study was conducted [DIR Art 107m(6)]. The study report should be submitted to the competent authority(ies) as soon as possible after its finalisation and within 12 months of the end of data collection.
Page 13 – section 10.6		Comment: Is not a summary of the AEs received during the study also required – it appears that all that is required is the management and reporting of AEs – yet this is the results section Proposed change (if any): clarification
Page 16 – Paragraph starting at line 564		Comment: What about nationally authorised products not done through DCP or MRP? For points a-c need to say that nationally authorised products will not go to PRAC Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 18th 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
French Association of Regional Pharmacovigilance Centres

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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 time of preparation of the protocol, the study duration, the year to submit the final report and the answers to the possible questions from competent authorities, guarantee to the MAHs enough time to ensure correct marketing campaign of their product. PASS included in RMP can be considered as a valuable protection against early withdrawal from the market risk.

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 290		Comment: Why suggesting that adverse events could be reported ? In PASS studies only adverse drug reactions are logically required. Reporting adverse events may lower signal detection efficiency. Proposed change (if any): “Management and reporting of adverse reactions”
Line 458		Comment: Why suggesting that adverse events could be reported ? In PASS studies only adverse drug reactions are logically required. Reporting adverse events may lower signal detection efficiency. Proposed change (if any): “10.6 Adverse reactions : management and reporting”
Line 588		Comment: What should be the time frame of such negotiation between different MAHs and the competent authority? What should be the time frame of the PRAC answer ? Proposed change (if any):
Lines 631-691		Comment : Curiously, no time frame is required from the MAHs, whereas answer from the competent authority or the PRAC is required within 60 days.

Please add more rows if needed.

17 April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

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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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')*
294		Comment: How does this differ from milestone dates required for the protocol? Proposed change (if any): Please clarify.
329		Comment: Please provide timeline for immediate notification of change in benefit-risk. Does this mean any change or only those with adverse effects on benefit-risk

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>
April 17th 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

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
	1- We would like to express our astonishment regarding the type of requirements defined in this module related to PASS, which seem to belong more to regulations that to Good Practices. See line 106 "These guidance and requirements should also be considered by marketing authorisation holders for studies developed and conducted outside the EU". 2- The extent of the PRAC powers seems to overlap with that of the SAWP and the CHMP, with regards to requiring and assessing protocols and study reports for PASS. Has this Committee being created to supersede CHMP when it refers to post-marketing studies?

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 106		Comment: We would like to express our astonishment regarding the type of requirements defined in this module related to PASS, which seem to belong more to regulations that to Good Practices. "These guidance and requirements should also be considered by marketing authorisation holders for studies developed and conducted outside the EU" Proposed change (if any): Delete all requirements with regards to the content of the PASS itself and refer to a clinical investigation guideline for PASS. .

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module VIII- Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	In the text the term ‘encourage’ is often used. Please clarify the meaning of this: Is the MAH obliged to do what is encouraged or is it a suggestion only? We would discourage the use of such terminology as it can be confusing, Additionally; we suggest this guidance remain consistent with the other modules in the use of “shall” and “should” as appropriate.
	The definition of PASS continues to be vague and specific examples would be beneficial to understand what the Competent Authority would consider a PASS. For companies who marketed over-the-counter, non-prescription product, it is unclear if any studies would qualify as a PASS. These products are generally considered safe and thus do not require a prescription; however, for example, over-the-counter products can be at risk for medication error or overdose. If a study was performed on labelling comprehension to evaluate how to prevent medication error (a voluntary risk management activity), would this be considered a PASS? Specific guidance for over-the-counter medicinal products would assist MAHs in whether or not they should consider voluntarily providing protocols, progress reports and end of study reports for some of the studies that are common with over-the-counter medicinal products.
	Since the guidance is different for a PASS that is voluntarily initiated or pursuant to an imposed obligation the guidance should be structured accordingly, ideally with separate sections for each situation

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 97 – 99		Comment: The scope described limits the guidelines and requirements in section VIII.B to those non-interventional PASS which are initiated, managed or financed by the MAH in the European Union. However, it would be proposed that this extended also to those initiated, managed or financed on behalf of the Marketing Authorization Holder. In many cases multiple companies, such as local representatives, partners, etc can be involved, which are not the MAH and this guidance should also apply in such situations. Proposed change (if any): Amend text "The guidance ~~and requirements~~ in section VIII.B applies to non-interventional PASS which are initiated, managed or financed by the marketing authorisation holder within the European Union, or through a third party on behalf of the marketing authorisation holder."
Lines 105-106		Comment: '..studies developed and conducted outside the EU' it is not clear from this sentence if non-EU post-authorisation studies with safety objectives not required by an EU competent authority are in scope. Proposed change (if any): Suggest modifying text in line 106: '...studies developed and conducted outside the EU, at the request of an

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		EU competent authority, or which are part of the EU RMP.'
Line 113		Comment: 'date on which the analytical dataset is first completely available' please define better the term 'completely' as this impacts the timelines for results submission. Proposed change: Amend text – '...is first completely available and if necessary validated'
Lines 174-186		Comment: Although the requirement to submit protocols to the member states where the protocol is conducted is understood, it would be preferred if such requirements, as well as the format and method through which these would be supplied would be harmonized. Proposed change (if any): Does the study protocol need be transmitted to all MS even if the study is only performed in a single country? Please clarify to which competent authorities the protocol has to be transmitted for single country or multi-country studies Clarify the statement protocol is sent "for information" (unless local regulation state otherwise).
Lines 210-211		Comment: At the time of protocol development it is not possible to include details on participating sites. Study feasibility and site selection are only performed after protocol development. Proposed change (if any): Changes on investigators sites should be considered as a non-significant amendment or the EU registry (or CT.gov) could be used for this. Site list is a document that can be updated many times throughout the course of a study.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 228		Comment: This line makes an incorrect reference to VIII.B.1. The correct reference should be VIII.B.2
Line 269		Comment: We question the relevance of this information. Specific data management and statistical methods would be relevant rather than software and hardware to be used. In addition at protocol development vendor selection still has to be initiated and this information is not available. Proposed changes (if any): Amend text to reflect this – "Data management and statistical ~~software programs and hardware~~ methods…"
Lines 320 – 322		Comment: The general approach that the substantial amendments to the study protocol implemented only after submission is agreed upon. However, within the Clinical Trial Directive, measures are available for urgent changes, to be notified subsequently. Proposed change (if any): Should similar possibilities be implemented here or is this process considered not applicable as these protocols by definition should not impact treatment? Please clarify.
354 – 357		Comment: From this guidance, as read in conjunction with Module VII.C.5.5 it is understood that comprehensive findings, as well as the actual progress reports from post-authorisation studies will be included in the PSUR (1600-1604). However, it is also stated that progress reports should not be initially submitted through the PSUR (1626-1627). As part of current practice, progress reports (e.g. annual or bi-annual reports) from registries are provided to the agency as part of Follow-up measures. Such as progress reports are not necessarily due at the time of the PSUR. The additional requirement of providing progress updates as part of the PSUR, potentially at a different time

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 the progress report, will add a significant additional burden for the MAH, with potentially little additional value. Proposed change (if any): As previously submitted progress and final reports will be part of the product (eCTD) lifecycle, it would be expected that reports will not be resubmitted but instead will be referred to from the PSUR.
Line 364		Comment: Study reporting to HA within 12 months from end of data collection. We need further clarifications regarding what is meant with 'end of data collection' as the definition in the relevant paragraph is not clear. Proposed change: Amend text accordingly "...and within 12 months of the end of data collection and if necessary data validation"
Lines 365 – 367		Comment: The submission of the Report to the Member state in which the study is conducted is understood. However, as this is not currently required in all member states, it would be preferred if a clear and harmonized process would be established through which such notifications would be made. Proposed changes (if any): Establish a clear harmonized process for such notifications.
Line 376		Comment: 'To the Agency and the national competent authorities, as applicable'. Need further clarifications regarding the term 'as 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')*
		Proposed changes (if any): Please clarify which national competent authorities are 'applicable'
Line 531		Comment: This section is not completely in line with section on lines 193-202. Proposed changes (if any): Amend the text so that is in line. "The marketing authorisation holder is ~~encouraged~~ should ~~to~~ ~~have~~ make publicly available in the ~~information on the study, including the study protocol, entered prior to the start of data collection into the electronic~~ register of non-interventional post-authorisation safety studies maintained by the Agency before the start of data collection. This information should include an English translation of the title of the study and of the abstract of the study protocol. In case of substantial amendments to the study protocol, the marketing authorisation holder ~~is encouraged~~ should make ~~to have~~ the revised study protocol ~~entered into the electronic~~ available in the study register (see also VIII.B.4. for cases where publication of the protocol could threaten the validity of the study or the protection of intellectual rights). At the end of the study, the marketing authorisation holder ~~is encouraged~~ ~~to have~~ should make the final study report ~~entered into~~ available in the electronic study register, including an English translation of the abstract."
Lines 548-552		Comment: Per the scope defined in VIII.B.1 the requirements defined in section VIII.B apply to PASS conducted within the EU, although it is recommended to consider these requirements in studies outside the EU. However, the distinction based on region is not made in VIII.C, regarding studies imposed by the competent authorities. This implies that all such studies would need to comply with this guideline. However, VIII.C does refer back to the requirements in VIII.B for details on e.g. the protocol and report. This creates an unclear situation for PASS imposed by EU competent authorities, but performed in non-EU countries.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 might concern, for example, studies already ongoing in other regions for the same product and similar safety concern. The requirements for such situations should be clarified. Proposed changes (if any): Text should be added to the current section to clarify this: 'The provision of VIII.C refer specifically to post-authorisation safety studies initiated, managed or financed by marketing authorisation holders pursuant to obligations imposed by a competent authority in accordance with Article 10 and 10a of Regulation (EC) No 726/2004 and Articles 21a and 22a of Directive 2001/83/EC. <u>These requirements also apply to studies conducted outside the EU, at the request of an EU competent authority, or which are part of an EU RMP.</u>'
Line 639		Comment: 'the PRAC will nominate a PRAC rapporteur'. It would be better if the PRAC rapporteur is the same rapporteur as for the marketing authorisation application and all evaluations as they will have the most expertise on the product.
Lines 660 – 664		Comment: The submission of the protocol and letter to the Member state in which the study is conducted is understood. Proposed changes (if any): A clear and harmonized process should be established through which such notifications would be made.

Please add more rows if needed.

March 16, 2012

Comments on

Guideline on good pharmacovigilance practices (GVP)

Module VIII – Post-authorisation safety studies (Draft 20/02/2012)

I consider this draft a very clear and complete document.

As a member of the steering committee of RegiSCAR I have anyhow a specific point to discuss.

RegiSCAR, member of ENCePP is a consortium devoted to the study of RARE and Severe Cutaneous Adverse Reactions. As indicated by its name it works as a Registry, i.e. non interventional studies, but also organizes the collection and conservation of biological samples.

Module VIII states that "*In this context* –non interventional PASS-*, interviews, questionnaires and blood samples may be performed as part of normal clinical practice*". I am afraid that it may be more complicated.

At present stage of knowledge the "*investigation of potential or identified risks factors*" should include pharmacogenetics analyses that need the collection of DNA. In addition for severe (and fortunately very rare) adverse reactions, PASS are the BEST OPPORTUNITY to collect additional blood samples (e.g. blood lymphocytes for in vitro studies of immunologic mechanisms of reactions).

Collection of such samples definitely needs the agreement of ethical committees and written informed consent from patients. To the best of my knowledge that is legally considered more than "normal clinical practice", but it would be very damageable to progression of knowledge on safety of medicines if PASS devoted to the risk of severe reactions were not assorted of collection of such samples.

I therefore suggest the inclusion of a few sentences 1) on the principle that PASS must schedule the collection of blood samples allowing extraction of DNA for any severe reaction and 2) that needs to be done in accordance with European laws and with patient informed consent.

Sincerely,

Jean-Claude Roujeau M.D.

Emeritus Professor of Medicine, UPEC (University Paris-Est-Créteil), France

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2012

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

Comments from:

Name of organisation or individual
Kuros Biosurgery AG

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	This guidance documents seem mostly targeted towards products that already have gained access to the market. However, given that the Introduction references the Directive 2001/83/EC relating to medicinal products for human use and not to the 2001/20/EC that determines the safety reporting process in clinical trials, the company proposes that the Agency clarifies whether these guidelines apply to product under investigation as well as marketed products. It would also be helpful that, if the guideline pertains in some ways to medicinal product under investigation, these specific chapters should mention clinical trials. It would also be useful to indicate when the processes should start, e.g. with the first human experience? It would then be advisable to use some of the provisions of the pharmacovigilance guidance in the product development phase already. The company would like to be reassured that the guidelines for safety monitoring and reporting during the post marketing phase are in alignment with the guidelines and directives for safety monitoring and reporting in the development phase. Consequently, EMA should consider making references to clinical trials regulations in these guidance documents.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The company very much welcomes the effort of the EMA in revising the pharmacovigilance legislation and publishing such extensive and comprehensive guidance on this subject. However, there is a concern that this is not paralleled by a similar effort from the authorities in other territories, especially the US-FDA. A lack of harmonisation would represent additional hurdles for manufacturers willing to enter international market.	
	Are the principles and the processes behind these pharmacovigilance guidelines applicable for devices as well as drugs?	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Version date: 20 Apr 2012 12:56:00

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

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

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Declaration:

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

E-signature and date on file: Dr David John Lewis, Global Head of Pharmacovigilance

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	We suggest that the requirements as laid are not applied retrospectively for any on-going PASS but rather to new studies only.
	Requirements for MAHs with respect to disease focused not medicinal product focused registries are not provided. For example the adverse event collection and reporting provisions focus on the studied medicinal product but for a disease based registry, it is not clear under these circumstances what the MAH obligations are.

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 only: 'encouraged to submit protocol prior to start of data collection to the NCA where the product is authorized and to Agency…..'. Does this apply to local PASS studies running in 1 EU country only or non EU studies. Proposal: Clarify that requirement to submit protocol to NCA should be where study is conducted
175		Comment/proposal: State that both voluntarily initiated and mandated PASS studies the protocol should be shared with EMA (encouraged in first case and required in second). This section should be referenced/linked in some way so section C.4.2 where the timeframes are indicated.
188		Comment: As per Volume 9A should indicate that the protocol sign off may be a QPPV delegated activity to nominated country Pharmacovigilance responsible at national level, with appropriate oversight. Proposal: retain Volume 9A text 7.3 (page 92). "The QPPV at EU level and/or, where applicable, the nominated person responsible for Pharmacovigilance at national level, should be involved in the review of protocols for all PASS, ……"
189		Comment/proposal: 'PV contact person' not clear who this is Proposed change: Make clear that this is the nominated person responsible for Pharmacovigilance at national level.
193-200		Comment: Making a PASS study protocol publically available (even with redaction) can result in a competitor using this knowledge to its benefit and lead to misinformation in social and news media.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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: Redacted summary protocols are preferable.
193 (and 531)		Comment: posting of study protocol and results to public register maintained by EMA. We agree with the need for maximum transparency and thus to post (protocol and results) information on publicly accessible registries. Proposed change: To avoid the need to post on multiple registries each with different data structures and requirements we would though request not to specify a given registry at this stage.
296		Comment: it is difficult to plan for publication ahead of time. If the plan is not to publish and then the MAH decides to publish, does this require a protocol amendment? Proposed change: Suggest deleting plans for publication from the protocol.
345		Comment: the title is progress report but previously language used was interim report (B.4.1.6 line232) – are the two equivalent? Proposed change: If the same, recommend that same language is used.
334		Comment: This sentence is not quite clear, 'this information should not affect the information in PSUR/RMP' given this information is anyway relevant to PSUR/RMP? Proposal: If it just means that the immediate communication should not affect proper inclusion of the results of studies …by means of PSUR and in RMPs, this would be clearer
422		Comment only: A discussion of bias should be listed under section 9.9 (statistical methods), line 428
496		Comment only: Publication of study results by investigators - Without disagreeing with the content we think publication rights are out of scope for these guidelines. We consider that contractual agreements between data owners (or sponsors) and investigators are a matter for the parties signing the agreement.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
504		Comment only: 'confidential information' – Does confidential mean patient identifiers or confidential to the company?
577		Comment: Concern about the way this section on the procedure for imposing PASS is written, PASS can be required by the Agency or a national authority. This could potentially result in many studies that one authority deems important, but the Agency or other national authorities do not. It is not clear what the role of PRAC is here…. "in case the PRAC is involved in the oversight of the study" (line 639) Proposed change: The involvement of PRAC in the oversight and coordination /adjudication of nationally requested or Agency requested should be strengthened. If a national authority believes a PASS is required, there should be a process whereby the authority discusses the rationale with PRAC and if they agree, the request is generated through PRAC. This suggestion does not impact a national authorities' ability to request risk assessments for single or aggregate ICSRs. That would not change.
616		Comment only: Need to link to the RMP Module.
645		Comment only: Not clear what "Any pre-submission meeting will not impact on the imposed timelines" means?
653		Comment only: We can agree to the 60 day turnaround times for endorsement/comment/objections from the rapporteur concerning a submitted study protocol, but would add that we understand that 60 days for comment is a maximum. We would also like to see a process for expedited approval described; this given that there are circumstances (pandemic, catching a vaccination campaign) when 60 days would be too long; especially if there

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

16th April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
OPTUMInsight

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E- 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')*
339-342		Comment: What are the minimum AE collection requirements for PASS involving primary data collection? As non-serious EEA AEs have to be expedited within 90 days according to Module VI, does this mean that non-serious AEs must be collected? Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18th April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
Outcome Europe sarl

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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 178-180		Comment: for PASS voluntary initiated by the marketing authorisation holder, how can the marketing authorisation holder be required to submit the protocol to the competent authorities of the Member States to which the study is conducted? In other words, which authority could request the the marketing authorisation holder to submit the protocol to the competent authorities of the Member States to which the study is conducted, if the study is voluntary initiated by the marketing authorisation holder? Proposed change (if any):
Lines 179 and Line 184		Comment: for PASS voluntary initiated by the marketing authorisation holder, the marketing authorisation holder may be required to ***submit*** the protocol to the competent authorities of the Member States to which the study is conducted. Whereas, for PASS initiated by the marketing authorisation holder pursuant to an obligation, the marketing authorisation holder must ensure that the protocol is ***notified*** to the Agency or the national competent authority. 1. Would be possible to clarify the meaning of "submit" Line 179? It may be considered as "submit for approval". In that case, the requirements for a PASS initiated pursuant to an obligation (*notification*) seem less exigent than for a PASS voluntary initiated (*submission [for approval]*). 2. According to VIII.C.4.2, the protocol should be assessed by the PRAC or the national competent authority if the study is conducted in one single Member State. After the letter of endorsement is issued by the PRAC or the national competent authority, the protocol is forwarded (for information) to the national competent authorities of the Member States to which the study is conducted. Line 184: the protocol is not just "notified" to the Agency, but submitted for approval.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 258-259		Comment: it is not clear what the interpretation of “data sources”, “instruments” and “measures” is. Does it include any Patient Related Outcome questionnaire, script to patients when patients need to be reached out for follow up for example? Would a validation of such material be required in any case? Proposed change (if any):
Lines 298-299		Comment: it is not clear why the principal investigator shall sign the ENCePP Checklist for Study Protocols? Does it refer to the principal investigator/(primary) lead investigator who has overall responsibility across all the sites for ENCePP studies? Principal investigator/(primary) lead investigator might not be designated for non-ENCePP studies. Proposed change (if any):

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
Procter & Gamble

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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

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 54		Comment: also include medicines that are non-prescription Proposed change (if any):
Page 11 – line 364		Comment: swap the order of the two sentences in this paragraph – it would read more clearly. Proposed change (if any): The marketing authorisation holder shall submit the final study report to competent authorities of the Member States in which the study was conducted [DIR Art 107m(6)]. The study report should be submitted to the competent authority(ies) as soon as possible after its finalisation and within 12 months of the end of data collection.
Page 13 – section 10.6		Comment: Is not a summary of the AEs received during the study also required – it appears that all that is required is the management and reporting of AEs – yet this is the results section Proposed change (if any): clarification
Page 16 – Paragraph starting at line 564		Comment: What about nationally authorised products not done through DCP or MRP? For points a-c need to say that nationally authorised products will not go to PRAC Proposed change (if any):

Please add more rows if needed.

30_03_2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
PAREXEL International

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	It would be helpful to the reader if the contents included a list of abbreviations used. The guideline would benefit from a flow chart that summarises the procedures for the different study types given that there are overlapping requirements for different types.

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 67		Comment: This states that non-interventional studies may include the use of interviews, questionnaires and blood samples as part of normal clinical practice. This option is currently available in Volume 9A but is inconsistently applied amongst Member States. Proposed change (if any): As such it is recommended that the possibility of more specific guidance be included.
Line 74		Comment: Proposed change (if any): Highlight this line as a sub-heading VIII.A.1.
Line 96 and 546		Comment: Section B covers non-interventional studies initiated voluntarily or those imposed by the regulatory authority. Section C.4-7 covers only the latter. Some information about imposed studies appears in both sections. Proposed change (if any): It is recommended that this be streamlined and only appear in section C. The title of Section C could then be revised so that it does not specifically refer to operation of the EY network but covers all aspects of imposed studies.
Line 109 and 113		Comment: Date at which a study commences is defined as the date of the start of data. Line 113: End of data collection is defined as the date on which the analytical dataset is first completely available. It is unclear what is intended by the term “completely available”. Proposed change (if any): Please clarify.
Line 115		Comment: Definition of substantial amendment: For consistency it is suggested that consideration be given to cross referring to relevant examples of substantial and non-substantial amendments found in the EU. Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 116		Comment: Protocol changes likely to have the possible impact suggested on participants could only occur in interventional studies . Proposed change (if any): Perhaps this comment should be qualified accordingly.
Line 301		Comment: This requires details of feasibility studies to be included in non-interventional study protocols. Data of this nature may of commercial sensitivity. Proposed change (if any): It is recommended that any such data be omitted or be included at a sufficiently high level to remove any such sensitive information.
Line 346		Comment: This states that for centrally approved products EMA or PRAC may request progress reports. This exceeds the remit of the legislation. While the guideline states that certain tasks are recommended but not mandatory (based on legislation) this is the only optional task that can be imposed by EMA or the PRAC. Proposed change (if any):
Line 376 and 378		Comment: This should cross refer to Article 107p.1 and 3 respectively in the Directive and the corresponding article in the regulation. Proposed change (if any):
Line 379		Comment: Suggest adding 'Reasons for early termination – if applicable' as a section in the study report. Proposed change (if any):
Line 682		Comment: The study sponsor is required to request any waiver for submission of a study report within 3 months of the anticipated submission date. Proposed change (if any): It is recommended that a timeline for response to the request be included such that the sponsor has sufficient notice that a submission is/is not required.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

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 VIII – Post-authorisation safety studies) is very comprehensive and provides helpful general guidance on the requirements for non-interventional PASS, protocol oversight, and transparency. 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.
	Provision for a pre-submission meeting with the Agency and the PRAC Rapporteur to clarify specific aspects of a requested study and design a scientifically-sound study is welcomed.
	Systematic literature reviews and meta-analyses should not be classified as ‘studies’. Systematic literature reviews and meta-analyses merely aggregate and summarize existing data derived from completed studies and do not generate new safety data. Under the proposed expanded usage of the term ‘study’ in the draft module, the Summary of Clinical Safety (SCS) would now constitute a separate “study” from the individual clinical trials that it summarizes. If the regulatory rationale for expanding the traditional definition of a ‘study’ is to require a MAH to conduct cumulative evidence reviews during the post-authorization period, this goal could be better accomplished through specific requests for a systematic literature review or meta-analysis from the PRAC or a competent authority. This approach would preferably be described in GVP Module VII (PSUR) rather than in Module VIII (PASS).

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)*
54-55 135-136		**Comment**: The definition of a non-interventional study (per EudraLex Volume 10) includes, *"medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorization"* (lines 54-55). Is this intended to imply that safety data for patients in whom the product is used in a manner that is not consistent with the SmPC are explicitly excluded from a PASS? This would seem inconsistent with a stated potential objective of a PASS (line 135-136): *"to assess patterns of drug utilisation and use of the medicinal product that may have an impact on its safety"*. This criterion (line 54-55) seems to exclude utilization studies of off-label use, which may be an important safety concern. **Proposed change**: Clarify the intended meaning of these sections so that they are consistent with each other.	
193-195 532-541		**Comment**: It is not clear where the Agency expects the MAH to publicly post a PASS protocol, abstract, and study report. Does "... electronic register of non-interventional post-authorisation safety studies maintained by the Agency" refer to the ENCePP study registry? Many MAHs currently register non-interventional PASS studies, including studies	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		involving primary data collection and also those using secondary data, at ClinicalTrials.gov. Posting and maintaining double listings for the same study would create inefficiency and an unnecessary burden. **Proposed change**: Revise lines 193-194 to read: "*The marketing authorisation holder is encouraged to make the study protocol publicly available in the register of non-interventional post-authorisation safety studies maintained by the Agency,* ***or in another electronic repository that is accessible from the EU,*** *before the start of data collection.* Also, revise lines 532-541 to read: "*The marketing authorisation holder is encouraged to have information on the study, including the study protocol, entered prior to the start of data collection into the electronic register of non-interventional post-authorisation safety studies maintained by the Agency,* ***or in another electronic repository that is accessible from the EU"****.*	
209-212 386-387		**Comment**: The guideline is unclear as to the distinction between "*Responsible Parties*" which was used as a section heading for the Protocol (line 209), and "*Investigators*" which was used as the section heading for the Final Study Report (Line 386). **Proposed change**:	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Include definitions for both "*Responsible Parties*" and "*Investigators*" in Section VIII.B.2 (Definitions) and in GVP Annex I (Definitions). These definitions should be consistent with one another and also clarify the specific roles of individuals who are included as Responsible Parties (e.g., primary author on the protocol), but who are not considered an Investigator.	
747 and 760		**Comment**: The distinction between sentinel sites and intensive monitoring schemes is not clear. For example, intensive monitoring schemes are possible in a set of sentinel sites. **Proposed change**: Define "*sentinel sites*" in section VIII.App1.1.1.1. (Sentinel sites) and define "*intensive monitoring schemes*" in section VIII.App.1.1.1.2. (Intensive monitoring schemes). Include both definitions in GVP Annex I (Definitions).	

16 April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

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 VIII – Post-authorisation safety studies.
	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')*
188 - 192		Comment: In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) (see Module I) should be involved in the review and sign-off of study protocols. Where applicable, the contact person for pharmacovigilance at national level should be informed of any study conducted in that Member State and receive a copy of the protocol. Proposed change (if any): In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) (see Module I) should be involved in the review and approval of study protocols. Where applicable, the contact person for pharmacovigilance at national level should be informed of any study conducted in that Member State and receive a copy of the protocol.
193 - 195		Comment: The marketing authorisation holder is encouraged to make the study protocol publicly available in the register of non-interventional post-authorisation safety studies maintained by the Agency before the start of data collection. Is the whole study protocol to be published or just a synopsis? Proposed change (if any):
328		Comment: risk-benefit Proposed change (if any): Benefit-risk; please use this term throughout the whole document

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
329 - 331		Comment: Any new information that might influence the evaluation… Proposed change (if any): Any new information the MAH becomes aware of that might influence the evaluation…
498 - 499		Comment: the marketing authorisation is encouraged to agree in advance a publication strategy with the principal investigator. Proposed change (if any): if the MAH becomes aware of the study he is encouraged to agree in advance in a publication strategy with the principal investigator
660		Comment: as appropriate as been issued Proposed change (if any): as appropriate has been issued
894		Comment: how a medicinal product is, prescribed and used Proposed change (if any): how a medicinal product is prescribed and used

Please add more rows if needed.

19.04.2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

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 here as well as questions for clarification that were raised while reviewing the draft modules. While the PRAC will have regulatory oversight for the review of protocol and final report for NI PASS, the new GVP guideline does not address the regulatory framework for interventional PASS and whether the new legislation will have any impact on the current CHMP and national HAs framework related to the review of these post-approval commitment safety studies and corresponding national CTAs.

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')*
192-194 **531-540**		**Will the agency provide more information and clarity on how this registry will operate? Which studies will be included, who will maintain; only EU studies or beyond?**

11 Apr 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

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
PASS to be notified to the CAs	General comments: PASS to be notified to the CAs, study protocol, can requested at any time 90 days timeline for non-serious cases arising from NIS
581	Requests for joint PASS, how to handle
610	Connection to RMP

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.

10-APR-2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
SANOFI Saudi Arabia

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	It is related to section VIII B.5.3. Study Report:- Prematurely termination or delayed termination due to potential safety signal was detected during the study is poorly presented in this section. However, it is common if the studied drug had incomplete safety data from previous clinical trials related to this drug. And this termination will greatly affect the current RMP related to the studied drug. Therefore I suggest to add a separate section for study termination which will give more focus on when HCP or MOH decided to terminate the study and how they notify EC & CA and the essential components off the report.

2. Specific comments on text

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

Please add more rows if needed.

17.04.2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
SciencePharma

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Could you please precise the format and mode of transmission of information concerning risk benefit balance described in v 329?
	Could you please specify what kind of format should progress reports and final study reports have (v 348, 368)?

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 VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Guidance for the transitional period is needed and it should be clarified how to deal with protocols which are already in review when this GVP becomes final.

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 67-68		Comment: In non-interventional studies some times it is necessary to apply interviews, questionnaires and blood samples. Proposed change intended to avoid possible misunderstanding that only interviews, questionnaires and blood samples performed as part of normal clinical practice are allowed Proposed change (if any): In this context, interviews, questionnaires and blood samples *appropriate for these types of studies* may be ~~performed~~ *considered* as part of normal clinical practice.
106-107		Comment: For studies in non EU countries, not performed for the EU RMP, which fall under the definition of PASS studies there can not be any obligation to follow the EU GVPs. Proposal: “These guidance and requirements *could* ~~should~~ also be considered….”
184-185		Comment: “Study protocols should be submitted to the agency or the national competent authority as applicable and the MS where the study is conducted.” For meta-analysis and systematic reviews there is no MS where the study is conducted. Proposal: add: *For meta analysis and systematic review the protocol only needs to be submitted to the Agency or the national competent authority, as 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')*
188-190		Comment: "In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) (see Module I) should be involved in the review and sign-off of study protocols." This should only be relevant for PASS protocols performed in EU and/or conducted undertaken pursuant to an agreed EU RMP. Proposal: "In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) (see Module I) should be involved in the review and sign-off of study protocols *conducted in the EU and/or undertaken pursuant to an agreed EU -RMP*."
190-192		Comment: "Where applicable, the contact person for pharmacovigilance at national level should be informed of any study conducted in that Member State and receive a copy of the protocol." This requirement is should only be applicable for studies performed or sponsored by the MAH. Proposal: "Where applicable, the contact person for pharmacovigilance at national level should be informed of any study*, sponsored or conducted by the MAH,* conducted in that Member State and receive a copy of the protocol."
237-238 and 397-399		Comment: It is possible that unpublished pertinent information exists that is not under control of the sponsor/MAH. The Sponsor/MAH may very well have undertaken all reasonable efforts to uncover such unpublished data, but an obligation to review of **all** unpublished data is not possible.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): "… and critical review of all available published *data* and unpublished data *only as available to the sponsors/MAH to* evaluat~~ing~~ pertinent information and gaps in knowledge that the study is intended to fill.
287-288		Comment: Document states. Protection of human subjects: safeguards in order to comply with national and EU requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies Proposed change (if any): Please provide reference to the legislative instrument and/or documents from which the Agency reads this obligation.
309		Comment: There is no reference to the definition of "substantial changes". If this is meant to be "substantial amendments" as defined in VIII.B.2, cross-reference to that section should be given. Otherwise it should be defined what "substantial changes" are. Proposal: Correct to cross-reference to "substantial amendments" or clarify the definition of "substantial changes".
321 + 670-671		Comment: Line 321 does not mention anything on approval of substantial amendments while lines 670-671 state that the MAH will be informed on endorsement or objection. Proposed change (if any): add approval process to line 321

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
516-517		Comment: "The marketing authorisation holder should ensure that all study information is handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of the records of the study subjects remains protected". It is not stated for how long this data should be kept by the MAH. Proposed change (if any): Clarification is needed on the retention time.
608-610		Comment: PASS could need more time than necessary for next PSUR Proposed change (if any): All post-authorisation safety studies imposed as a condition to the marketing authorisation will be described in the RMP (see Module V) and their results provided in the next PSUR *after finalisation of the final report* (see Module VI), where applicable.
660-662		Comment: "Study protocols should be submitted to the agency or the national competent authority as applicable and the MS where the study is conducted." For meta-analysis and systematic reviews there is no MS where the study is conducted. Proposal: add: *For meta analysis and systematic review the protocol(s) only need(s) to be submitted to the Agency or the national competent authority, as applicable. There is no need to forward the letter of endorsement.*
677		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')*
		It is not clear when a waiver could be applicable. Proposed change (if any): State where/whether waivers could be appropriate.
682-686		Comment: Nothing is described about the way national competent authorities should work. Proposed change (if any): It would be useful to see guidance on the harmonisation of practice between different countries.

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

Name of organisation or individual
Medicines and Healthcare Products Regulatory Agency (Inspection, Enforcement & Standards Division)

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	Outcome *(To be completed by the Agency)*
Carrie	In places, this module refers to CAPs (centrally authorised products) as “products authorised pursuant to Regulation (EC) No 726/2004” whereas Module II refers to them simply as “centrally authorised products” e.g. lines 438, 584 , 589; the latter is preferable as it is much simpler and easier to read. I am not sure whether there is any particular relevance to the different terminology used, but in my opinion it seems to be inconsistent. In fact Module VIII uses a mixture of the two terms Authorised pursuant to… is used on lines 178, 317, 332, 347, 371 centrally authorised… is used on lines 565, 574, 704(x2), 712	
Anya	Consistency is required across the GVPs with respect to whether the term "risk-benefit" or "benefit-risk" is used. In this module: • Benefit-risk is used on lines 292, 333, 350, 557, • Risk-benefit is used on lines 17, 326, 328, 489,	

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)*
98	Anya	Comment: "financed by the marketing authorisation holder " Although this is the wording in the Directive, an MAH may provide funding to an investigator who wishes to run their own trial. In this circumstance, the MAH is not the sponsor of the trial (and has no control over its conduct) and it is not clear whether the PASS requirements apply to the MAH for investigator-initiated trials. However, we would expect an agreement to be put in place for the exchange of safety data between the investigator-sponsor and the MAH (funder). It may be useful to clarify this scenario in the GVP. Proposed change (if any): Not possible to propose a change until the requirement has been clarified.	
148-153	Anya	Comment: "studies that are funded by a marketing authorisation holder…" As above. It should be clarified whether this applies to investigator-initiated studies where the investigator and not the MAH is the sponsor of the study, but the MAH provides a funding grant. My understanding is the Directive requirements apply to MAHs and not to investigator-sponsors. MAHs do not have control of such studies, although agreements should be put in place between the MAH and the investigator-sponsor (it is the investigator-sponsor who develops the protocol and runs the	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		trial). The concept of sponsorship is missing here. Proposed change (if any): Not possible to propose a change until the requirement has been clarified.	
189-190	Anya	Comment: “the qualified person…review and sign-off of study protocols” This is not a legal requirement in the new legislation. Does QPPV sign-off apply only for PASS initiated pursuant to an obligation or for all PASS initiated by the MAH? Can the QPPV delegate this review and sign-off e.g. to a product medical expert, providing that the QPPV is made aware of the study? Proposed change (if any):	
204 and following headings	Anya	Comment: Is this format required for PASS that are not requested as an MA obligation and which are only conducted at sites outside the EU, for products that are authorised in the EU? Proposed change (if any):	
225-228	Anya	Comment: Amendments and updates will not be part of the initial protocol. Is the suggestion that a blank section 5 should be included in	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		the initial protocol, with updates being included as they occur? Proposed change (if any): Additional text *"This section should be left blank in the initial protocol, with updates being included in subsequent versions as they occur."*	
229-235	Carrie	Comment: Milestones - in updated versions of the protocol, should planned dates be changed to actual dates, where milestones have been reached, or should actual dates be added alongside the planned dates to show whether or not milestones where accomplished on time? Proposed change (if any):	
287-289	Anya	Comment: "ensuring the well-being and rights of participants…" Protection of human subjects. If the PASS involves retrospective review of medical records, this may be less relevant. For prospective PASS, confidentiality of participants may need to be considered in addition to well-being and rights. Proposed change (if any): *"ensuring the well-being, rights and confidentiality of participants…"*	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To 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)*
327-329	Anya	Comment: "The marketing authorisation holder shall monitor the data generated while the study is being conducted and consider their implications for the risk-benefit balance of the medicinal product concerned" Again, the MAH can only do this for studies that it sponsors not for investigator-initiated studies, which the MAH has no control over, but for which the MAH may provide funding. Proposed change (if any):	
379-380	Carrie	Comment: "If a study is discontinued, a final report should be submitted and the reasons for terminating the study should be provided." Would it be useful to reiterate the timeline for submission here (which I assume is within 12 months of the end of data collection as mentioned in line 365). Proposed change (if any):	
414	Carrie	Comment: "Diagnostic criteria <u>are provided</u>, if applicable." Amend this to "*Diagnostic criteria <u>should be</u> provided, if applicable"* Proposed change (if any):	
474	Carrie	Comment: "Generalisability" is this actually a word?? Surely there must	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		be a better term available, particularly considering that English is not the first language for many people who will be reading this. Proposed change (if any):	
622-623	Anya	Comment: "The marketing authorisation holder has the responsibility to ensure that the study is not a clinical trial, in which case Directive 2001/20/EC shall apply." This sentence construction is unusual. PASS can be interventional studies (clinical trials). The obligation is for the MAH to ensure that if the study is interventional it is conducted in accordance with Directive 2001/20/EC. Proposed change (if any): *"It is the marketing authorisations holders responsibility to identify studies which are interventional i.e. clinical trials, and where applicable ensure that they are conducted in accordance with Directive 2001/20/EC."*	
665-666	Anya	Comment: "EU and national requirements shall be followed to ensure the well-being and rights of participants in the study" Any confidentiality? Proposed change (if any): "*to ensure the well-being, rights and confidentiality of participants…"*	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To 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)*
869	Anya	Comment: Spelling mistake “provisionss” Proposed change (if any): “provisions”	
		Comment: Proposed change (if any):	

Please add more rows if needed.

<18 April 2012>

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

Comments from:

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

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

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
T l phon +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.euro a.eu **Websi e** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	ENCePP Checklist There are concerns referring to the above mentioned checklist: 1) Is the checklist up to date regarding the new legislation or do we refer to an old checklist in line with Volume 9a? 2) Is this a regulatory controlled document? Who is responsible /liable for changes of this checklist? Therefore it is proposed that only legally controlled checklists published by the Agency should be mentioned and referred to in the GVP module.
	Words like “encouraged” should be avoided in the GVP modules in connection with regulatory provisions.
	The scope of a PASS is defined very broadly in lines 40 – 43. It includes “characterizing or quantifying a safety hazard” and “confirming the safety profile of the medicinal product”. It can be argued that from a certain size onwards any phase IV study or NIS that a MAH might want to conduct would meet these criteria and should therefore be classified as a PASS. To avoid such misconception detailed guidance is needed on how to differentiate between an actual PASS and an ordinary phase IV study or NIS.
	The main focus of Module VIII is to provide guidance for MAHs an how to plan, conduct, analyse and report a PASS imposed by a competent authority in cooperation with this and other concerned European authorities. Repeatedly, however, the document recommends that a MAH should adopt the same principles when planning to conduct a PASS voluntarily and to inform authorities about the project in the same way as is required for an imposed PASS. While this seems reasonable it should also be clarified that any documents relating to a voluntary PASS are shared with authorities for information only and that authorities are not encouraged or entitled to come back to the MAH to discuss protocols, request or mandate changes of study objectives, suggest or impose specific methods of data collection and analysis etc.
	The title of the document implies that it covers all PASS, however this is not the case and therefore the title is misleading. The

Stakeholder number *(To be completed by the Agency)*	General comment
	document gives guidance for non-interventional PASS and the process for imposing any PASS. Interventional PASS are otherwise covered by the clinical trials directive and volume 10. The document title should be updated to reflect this and the introductory text clarified. Generally the process for voluntary PASS versus imposed PASS is not always clearly differentiated within the document. The document is confusing in places and would benefit from the addition of a flowchart describing the different pathways for the request of a PASS and review of documents relating to them etc. In addition the section VIII.C.4.2. would be better placed nearer the beginning of the document in order add context early on.

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 44-45		Comment It is unclear whether this means any authority or authorities of the EU member states. This should be clarified. Proposed change (if any): A PASS may be initiated, managed or financed by a marketing authorisation holder voluntarily, or pursuant to an obligation imposed by a competent authority of the Member State,
Lines 108-118		Definitions: It would be helpful if these were in-line with those established in Volume 10 and the Clinical Trials Directive.
Lines 160 - 162		Comment: As non serious adverse reactions have to be submitted to authorities within 90 days, the provisions should be adopted as the ENCePP requirements might not be up to date. Receipt of non serious adverse reactions in a PASS at study end or time of CRF completion may result in work overload in a short timeframe and delay of identifying potential signals. Proposed change (if any): - provisions for meeting the marketing authorisation holder's pharmacovigilance obligations, including the reporting of serious and non serious adverse reactions and other safety data by investigators, if applicable;
Lines 174-179		Comment: The wording "is encouraged" is a week expression not usable for inspections as expectations might be assessed as "shall" by inspectors. It should be clearly stated that the protocol submission to the Agency and/or NCA should be based on what

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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 Agency expects as well as the NCA in their local regulation. Proposed change (if any): For PASS voluntarily initiated by the marketing authorisation holder, the marketing authorisation holder ~~is encouraged to~~shall transmit the protocol prior to the start of data collection ~~to the national competent authority of the Member States where the product is authorised and~~ to the Agency for PASS concerning products authorised pursuant to Regulation (EC) No 726/2004~~. The marketing authorisation holder~~ and may be required by the national competent authority to submit the protocol prior to the start of data collection to the competent authorities of the Member States in which the study is conducted [DIR Art 107m(5)] or to the national competent authority of the Member States where the product is authorised.
Lines 175-176		"...to the national competent authority of the Member State where the product is authorised" in line 176 is unclear. This may mean a large number of transmissions for a single product which is authorised throughout Europe and may not be practical. If the intention is to send the transmission to the Member states in which the study is to be conducted this should be clarified. These types of statements are made throughout the document and should be considered carefully and if possible clarified. If the MAH submits a protocol voluntarily, it is unclear if the MAH must await a response before proceeding with a study. This should be clarified.
Lines 185-186		Translation is relevant only for local studies where the protocol is written in local language.
Lines 187-191		Comment: When local contact persons for PV should just receive the protocol or be informed about a study, country specific requirements cannot be reviewed (e.g. differences in labelling for non centrally, or MR approved

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		products, understanding of “non interventional“ practices. Proposed change (if any): In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) (see Module I) should be involved in the review and sign-off of study protocols. Where applicable, the contact person for pharmacovigilance at national level should be involved in the review of the study protocol but at least informed of any study conducted in that Member State and receive a copy of the protocol.
Line 196		It is not clear what kind of protocol amendments could be helpful or would be acceptable in the described situation.
Lines 209-211		For large phase IV studies or NIS it is often necessary to recruit additional study centres during the course of the project. It is therefore not feasible to include all investigators in the initial version of the protocol. Amendments to update the list must be an option.
Line 228		Topic “Milestones” Comment: It is not practical to include all milestones in the protocol as these may change frequently and then – due to this requirement – require frequent inappropriate protocol updates. The interim analyses provided will include the requested information. Proposal: Removal of this requirement is proposed.
Line 231		Should only be applicable for PASS requested by a CA. A CA should not be entitled to request progress reports for a voluntary PASS after the protocol has been submitted (see general comment No. 4).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 251-252		Systematic reviews and meta-analyses are not normally classified as “studies” and regulations for patient informed consent and data privacy are not applicable.
Chapter VIII.B.4. compared to lines 666-673		Comment In Chapter VIII B 4 the PRAC is not mentioned and authorities that may need to receive protocols are precisely mentioned. Whereas starting at line 666 the procedure of submission of substantial amendment is not totally aligned to chapter VIII.B.4. Proposed change (if any): Alignment requested in lines 666-673: After a study has been commenced, any substantial amendments to the protocol shall be submitted before their implementation, to the ~~national competent authority or to the PRAC, as appropriate (see VIII.B.1. for the definition of a substantial amendment)~~ Agency for PASS concerning products authorised pursuant to Regulation (EC) No 726/2004 and may be required by the national competent authority to submit the protocol prior to the start of data collection to the competent authorities of the Member States in which the study is conducted [DIR Art 107m(5)] or to the national competent authority of the Member States where the product is authorised. The national competent authority ~~or the~~, represented by the PRAC, as appropriate, shall assess the amendments and inform the marketing authorisation holder of its endorsement or objection [DIR Art 107o]. In case of PRAC involvement, the marketing authorisation holder should submit the amended protocol to the Agency together with a letter of justification for the proposed amendment. This request will be evaluated by the PRAC and a letter of endorsement or objection will be provided to the marketing authorisation holder within 30 days of submission.
Lines 313-316		Comment: see comment concerning lines 174-179

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): For PASS voluntarily initiated by the marketing authorisation holder, the marketing authorisation holder ~~is encouraged to~~should transmit the updated protocol to the national competent authority of the Member States where the product is authorised, and to the Agency for PASS concerning products authorised pursuant to Regulation (EC) No 726/2004.
322 - 323		Comment: The wording “encouraged” is too week and should be replaced by “should”. Proposed change (if any): The marketing authorisation holder ~~is encouraged to~~should have updated study protocols entered in the register of non-interventional post-authorisation safety studies maintained by the Agency.
Lines 326-333 (328)		“Any new information that might influence the evaluation of the risk-benefit shall immediately be communicated” requires further explanation as, for database studies, data are frequently provided to the MAH at preset dates, which may be several months after the event. Proposed change: Any new information that the MAH becomes aware of that might influence….. In addition the phrase “Any new information that might influence the evaluation of the risk-benefit balance...” is very broad. This could be interpreted as a requirement to immediately report all potential new safety information even if it has a low public health impact and may only lead to a minor labelling update (if any in case the new information is subsequently confirmed to be not valid or not strong enough to support a labelling change). Proposed change:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		To avoid that the authorities will receive inappropriately many notifications we suggest changing this phrase to "Any new information that might significantly impact public health", "Any new information that might significantly change the risk-benefit balance" or similar text.
Line 345ff		See general comment No. 4; it is not clear whether progress reports can be requested also for PASS conducted voluntarily by a MAH.
Line 363ff		See general comment No. 4; submission of a final report is mandatory for an imposed PASS only!
Lines 367-370		Comment This indicates that the MAH will be 'encouraged' to transmit the final study report to the relevant competent authorities for PASS voluntarily initiated by the MAH. However, to meet the legal requirement set out in Art. 107m (6) of Directive 2001/83/EC the MAH does not have a choice to transmit the final study report because the MAH "shall send the final report (…) within 12 months of the end of data collection." Proposed change (if any): For PASS voluntarily initiated by the marketing authorisation holder, the marketing authorization holder ~~is also encouraged to~~should transmit the final study report to the national competent authority of the Member States where the product is authorised when requested by natonal competent authorities in their local regulations, and to the Agency for PASS concerning products authorised pursuant to Regulation (EC) No 726/2004.
Line 492		Comment The wording "encouraged" is too week and should be replaced by "should". Proposed change (if any): The marketing authorisation holder ~~is encouraged to~~ should have the final study report entered in the register of non-interventional post-authorisation safety studies maintained by the Agency, including an English

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		translation of the abstract.
Line 497		The word “holder” needs to be inserted Proposed change (if any): “…marketing authorisation holder, the marketing authorisation holder is encouraged to agree in advance a…”
Lines 496-504		It is unclear whether this paragraph is applicable also for a PASS imposed by a competent authority but finally conducted by independent investigators.
Lines 506-508		Comment The wording “encouraged” is too week: Original text: The marketing authorisation holder is encouraged to transmit the final manuscript of the article to the Agency and the competent authorities of the Member States in which the product is authorised within two weeks after acceptance of the publication. Proposed change (if any): The marketing authorisation holder ~~is encouraged to~~ should transmit the final manuscript of the article to the Agency and the competent authorities of the Member States that expect this transmission in their local regulations in which the product is authorised within two weeks after acceptance of the publication.
Lines 531-538		Comment The wording “encouraged” is too week and should be replaced by “should”. Proposed change (if any): The marketing authorisation holder ~~is encouraged to~~ should have information on the study, including the study protocol, entered prior to the start of data collection into the electronic register of non-interventional post-

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		authorisation safety studies maintained by the Agency. This information should include an English translation of the title of the study and of the abstract of the study protocol. In case of substantial amendments to the study protocol, the marketing authorisation holder ~~is encouraged to~~ should have the revised study protocol entered into the electronic study register (see also VIII.B.4. for cases where publication of the protocol could threaten the validity of the study or the protection of intellectual rights.
Lines 531-532		See general comment No 4. It is unclear whether study registration is mandatory for an imposed PASS.
Lines 587-592		Key elements The phrase (line 591) “These key elements may then be imposed on all marketing authorisation holders” should be clarified as it may imply that joint PASS may be imposed rather than just particular key elements of the study design. Enforcing a joint PASS may be unrealistic considering likely differing safety profiles, indications, patient populations, formulations, etc of different companies’ products and resultant biased comparisons in results. A request for individual companies to perform separate PASS for the same risk may be more achievable than a single PASS conducted by multiple companies.
Lines 596-604		It is unclear whether the paragraph also refers to paragraphs a and b (lines 561-575) and entitles MAHs to comment in other situations. This should be clarified.
Lines 610-611		RMPs are very comprehensive documents. It is unclear whether a complete RMP needs to be written for old products in case a PASS is set up to clarify a specific safety aspect.
Line 649ff		The PRAC will have oversight of most aspects of safety for centrally authorised products and in some instances also other products. Therefore it seems inconsistent that they do not consider, or have oversight 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')*
		interventional PASS.
Line 659		A typo needs to be corrected. Proposed change (if any): … PRAC, as appropriate has been issued …
Lines 693-697		Comment: The request to submit any necessary variation with the final study report within 12 months of the end of data collection may be very difficult to implement since, once the study report is available, some time is needed to prepare the variation package. In addition, the PASS may trigger a labelling change of minor relevance (such as the addition of one non-serious ADR) and it may be inappropriate in terms of economy and practicality to immediately file a variation due to this one change alone instead of combining potential new risks arising from other sources. A risk based approach should therefore be introduced. Proposed change: The marketing authorisation holder shall evaluate whether the results have an impact on the marketing authorisation and shall, if necessary, submit to the national competent authorities or the Agency an application to vary the marketing authorisation [DIR Art 107p(2)]. In such case, depending on the importance of the risk for public health and the benefit risk profile of the product, a reasonable timeline for submission of the variation to the national competent authority or the Agency should be chosen. In cases of an important risk submission together with the final study report within 12 months of the end of data collectionshould be aimed for. Any minor finding which leads to an addition of a new minor side effect may be introduced by variation within 12 month after submission of the final report unless either the QPPV or the NCA request different based on the assessment of the finding.
Line786ff		This raises issues of data privacy and data protection that need to be adequately addressed.
VIII. C 545 ff		See general comment No 4; results should not be assessed by PRAC (line 686 ff) and no 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')*
		suspension of revocation of marketing authorization should be imposed as consequence of a voluntary PASS (lines 699–702).

Please add more rows if needed.

17 April 2012

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies' (EMA/813938/2011)

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
	PASS: Which studies are in and out of scope? Initiatives with commercial aspects should no longer be allowed. But Marketing & Sales may initiate other initiatives such as patient support programmes or other studies that are not PASS. Do they fall within the scope of GVP? Or is ensuring the collection of (S)AE and special cases (passive surveillance) enough? Where is the border between PASS voluntarily initiated by MAH and other post marketing studies not being PASS? More guidance would be 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')*
112		Comment: End of data collection: Provided definition is different from GCP and therefore source for confusion. Proposed change (if any): Harmonize with GCP and the rest of the document. LPLV and 12 months thereafter the final study report must be final. If needed add a separate wording for retrospective reviews.
112		Comment: reference: IM Annex IV.I.3 Where does this refer to? Proposed change (if any):
345		Comment: Progress report may be requested… what is the purpose? Studies (and exposure) are also discussed in DSURs. Why the duplication? Proposed change (if any): Please delete

Please add more rows if needed.