26 October 2015
EMA/710492/2015

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

GVP Module VIII – Post-authorisation safety studies (Rev 2) (EMA/813938/2011)

The draft of this module was released for public consultation between 11 August and 9 October 2015. The module has been revised, taking the comments received into account.

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

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

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

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8 October 2015

Submission of comments on GVP Module VIII – Post-authorisation safety studies (Rev 2) (EMA/813938/2011)

Comments from:

Name of organisation or individual
ACRO (Association of Clinical Research Organizations)

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 110,000 employees engaged in research activities around the world (including 30,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 research sponsors annually. ACRO welcomes this opportunity to comment on the draft revision of the Module VIII guidance on non-interventional post-authorisation safety studies (PASS). ACRO is concerned that requirements for the regulation of PASS have become unnecessarily complex and provide a potential source of compliance risk, both for	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	organisations conducting PASS and for competent authority staff involved in their regulation. PASS requirements are detailed across numerous documents (pharmacovigilance legislation, guidelines on good pharmacovigilance practices, Regulation (EC) No. 1234/2008 on variations, post-authorisation measures: questions and answers, Periodic Safety Report (PSUR) and Risk Management Plan (RMP) templates, and fees legislation). Confusion resulting from this complexity has led to inconsistent implementation of the requirements by organisations conducting PASS and to inconsistent application of the requirements by competent authorities. ACRO recognises and welcomes that the current proposed revisions are intended to make clearer the requirements of the current Module VIII PASS guideline. In particular, ACRO welcomes and supports the approach to distinguish legal requirements from recommendations (while noting that, in practice, more could be done to improve the document in this regard). However, ACRO is disappointed that the opportunity has not been taken to produce a guidance document that pulls together, in a clear and consistent way, all of the requirements relevant to PASS arising from the different source documents. While recognising the scale this task, ACRO recommends and encourages the EU regulatory network	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	to undertake such an initiative. ACRO also recommends and encourages the network to reach agreements on simplification of the PASS requirements, consistent with the legislation. Together, these initiatives would greatly improve the understanding of and compliance with PASS requirements.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 106		Comment: ACRO welcomes and supports the addition of the clarification that collection of blood samples maintains the non-interventional status of a PASS. Proposed change (if any):	
Lines 124 - 128		Comment: ACRO welcomes and supports the proposal to make a distinction in the text of the guideline between legal requirements and recommendations. However, on reviewing the guideline, ACRO saw little evidence of this distinction in practice and recommends that the draft guideline is further amended to highlight these differences. Proposed change (if any): Further amend the draft guideline to ensure this distinction is made clear whenever appropriate.	
Lines 150 - 155		Comment: The list of changes given as examples that may be considered substantial amendments of the protocol is very high level. Within each category, there may be some changes that do and some that do not constitute a substantial amendment. This gives scope for differing interpretations between study sponsors, between competent authorities, and between sponsors and competent authorities. Consequently, ACRO recommends that a more precise list of changes that will be considered to be substantial amendments should be	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		developed. Proposed change (if any): Include a more precise list of changes that will be considered substantial amendments.	
Line 162		Comment: Directive 2001/83/EC as amended by Directive 2010/84/EU defines a PASS in Article 1(15) as “any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.” This legal definition expressly does not include the use of other interventions, which are outside the scope of the Directive. ACRO therefore recommends that the phrase “class of medicinal product or other intervention as appropriate” is changed to “or class of medicinal product as appropriate.” Proposed change (if any): Change the phrase “class of medicinal product or other intervention as appropriate” to “or class of medicinal product as appropriate.”	
Lines 212 - 221		Comment: The pharmacovigilance legislation requires the EMA to publish in a publicly available register the protocols and abstracts of results of PASS imposed as an obligation by a competent authority. It also specifies that the final reports of such studies must provide the date of registration in this register. The EMA recommends that information about PASS which are initiated, managed or financed voluntarily by a MAH	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		and which are required in the Risk Management Plan (RMP) to further investigate safety concerns or to evaluate the effectiveness of risk minimisation activities, or any other PASS should also be entered into this register in order to support the same level of transparency, scientific and quality standards. While ACRO recognizes and supports the concept of applying similar standards to all PASS, irrespective of the regulatory status of the study, ACRO is not aware of any legal basis that mandates registration of studies conducted outside the EU and which are not part of the EU RMP. The distinction between legal requirements and recommendations is not clear in this section of the draft guideline, and ACRO recommends that the text is modified accordingly. Proposed change (if any): Revise the proposed text to ensure that legal requirements and recommendations concerning use of the EU PAS Register are made clear.	
	Lines 225 - 228	Comment: ACRO welcomes and supports the proposed flexibility to permit redaction of the protocol that is made publicly available when necessary to protect the integrity of the study or intellectual property. ACRO is aware that this is an important issue for many PASS sponsors. Proposed change (if any):	
	344 - 358	Comment: ACRO welcomes and supports the proposed flexibility to justify the non-collection and/or non-expedited reporting of certain adverse events. In addition to maintaining	

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		the integrity of outcome studies, this will allow for simplification of study procedures to focus on the important risks. Proposed change (if any):	
Lines 421 - 425		Comment: The proposed text states that safety findings should be reported in Periodic Safety Reports (PSURs) and Risk Management Plans (RMPs). However, ACRO notes that guidance on the PSUR relative to findings from non-interventional studies states “This section should summarise relevant safety information or information with potential impact on the benefit or risk evaluations” (HMA/EMA Guideline on Good Pharmacovigilance Practices Module VII – periodic safety update report (Rev 1) and ICH E2C(R2) guidance: Periodic Benefit-Risk Evaluation Report). Similarly, the RMP should be proportionate to the identified risks (HMA/EMA Guideline on Good Pharmacovigilance Practices Volume V – risk management systems) and therefore focus on those risks identified as important and so, again, only relevant information (including information on the effectiveness of risk minimisation measures) should be summarised in the RMP. ACRO therefore recommends that the proposed text is revised to make clear that only relevant PASS findings or information with potential impact on the benefit-risk evaluation should be summarised in PSURs and RMPs. Proposed change (if any): Revise the text to make clear 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')*	Outcome *(To be completed by the Agency)*
		only relevant PASS findings or information with potential impact on the benefit-risk evaluation should be summarised in PSURs and RMPs.	
Line 583 AND Lines 589 - 590		Comment: It is not clear what the sentence "This provision should be applied to all PASS" means. Is it a legal requirement for all PASS or a recommendation? ACRO recommends that clearer wording is used. Proposed change (if any): Make clear whether the provision is a legal requirement or a recommendation for PASS that are not imposed by a competent authority.	
Lines 648 - 653		Comment: There may be circumstances in which multiple MAHs do not agree to conduct a joint protocol. Consequently, ACRO recommends that these lines are not deleted as proposed but are retained to describe how the competent authorities will act under such circumstances Proposed change (if any): Retain the text that is proposed to be deleted. ACRO thanks the EMA for the opportunity to submit comments on this consultation. Please do not hesitate to contact us if we can provide additional information [redacted]	

Please add more rows if needed.

9 October 2015

Submission of comments on GVP Module VIII – Post-authorisation safety studies (Rev 2) (EMA/813938/2011)

Comments from:

Name of organisation or individual
AESGP

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	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)*
Page 4, lines 93-99		Comment: It is not clear which of these scenarios apply also to non-prescription products, as it specifically states “prescribed”. If they all apply, then the wording should be amended to indicate this more clearly. Proposed change (if any):	
Page 9, line 289		Comment: Proposed change (if any): **Rationale and background**: short description of the safety hazard(s), the safety profile or the risk management measures that led to the initiation or imposition of the study, and short critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.	
Pages 23-28		Comment: **Chapter VIII - Appendix 1: Methods for PASS studies** Several sections of this Chapter seem very Rx-focussed (with the use of words such as “prescription” and “prescribed”), so it should be clarified whether this section equally applies to OTC products. Proposed change (if any):	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25th September 2015

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP) - Module VIII – Post-authorisation safety studies (Rev 2)' (EMA/813938/2011)

Comments from:

Name of organisation or individual
AstraZeneca/MedImmune

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
84-85		Comment: The introduction states that studies to evaluate effectiveness of risk minimisation activities are PASS. However GVP XVI B.4 states that such guidance does not apply to the measurement of process markers. Please clarify if this exclusion in GVP XVI only applies to process markers that are not studies and that any study that is a process marker is a PASS. Proposed change (if any):	
93-94		Comment: Non interventional studies may be conducted to look at off-label use but such a study would not meet these criteria Proposed change (if any): The medicinal product is (are) prescribed in the usual manner according to current clinical practice.	
Lines 216-218:		Comment: Regarding the statement: "Registration in the EU PAS Register also applies to studies conducted outside the EU, including non-interventional 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)*
		requested by non-EU regulatory authorities." Is this saying that a drug utilization study or a comparative effectiveness study in, for example, the US and not as a requirement for the FDA would need to be registered? Proposed change (if any): Registration in the EU PAS Register also applies to studies conducted outside the EU and it is recommended to include non-interventional studies requested by non-EU regulatory authorities.	
600-602		Comment: Section III.4.4 of the RMP template 'Stated additional pharmacovigilance activities' requires category 4 PASS to be summarised in a specific table. This is not consistent with this text in GVP VIII which only requires them to be included in the summary table of pharmacovigilance activities Proposed change (if any):	
Line 885:		Comment: Regarding the statement: "Registries should normally not be used to demonstrate	

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		efficacy of a medicinal product." It is unclear why this approach cannot be taken since a well constructed registry could be used as a place to embed a trial to demonstrate efficacy. Proposed change (if any): Registries as an observational design should not be used to demonstrate efficacy of a medicinal product.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 Oct 2015

Submission of comments on Guideline on good pharmacovigilance practices (GVP) – Module VIII – Post-authorisation safety studies (Rev. 2) – EMA/813938/2011 Rev. 2

Comments from:

Name of organisation or individual
EFPIA [redacted]

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	EFPIA welcomes the opportunity to comment on this GVP module and addendum. In general we would like to express our concern that the issues raised and proposals formulated by EFPIA in its position paper of March 2015 appear to have been omitted in most parts. This position paper stressed the need for a fundamental discussion on the interpretation of the current regulatory framework concerning PASS, which EFPIA is missing in the proposed update of Module VIII. We would like to stress the importance to consider our key concerns explained below, which we believe would address the questions and unclarities currently experienced by EFPIA members, and we believe partly by regulators, too. **PASS definition** The current definition of PASS (Directive 2001/83, Article 1 (15)) is very broad and, due to the lack of a further definition on what constitutes a “safety hazard” either in the legislation or the GVP Modules, is open to inconsistent interpretation. The scope of the current PASS definition should be limited to studies aimed at addressing important risks, missing information or effectiveness of risk minimization: or in other words an EU-defined safety hazard. The scope of the definition should not include routine safety surveillance such as PMS studies in Japan, Korea, Brazil, nor clinical trials with several objectives including some related to safety. In order to correctly define the scope of PASS, GVP Module VIII should clarify that, for the purposes of PASS, the term	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	"safety hazard" relates to important risks and missing information listed in the safety specification of the EU-RMP. The current update does not define a safety hazard and does not address the issues with the scope of the PASS definition (e.g. concerning Non-EU PMS studies). The addition (in VIII.B.2.) that "Registration in the EU PAS Register also applies to studies conducted outside the EU, including non-interventional studies requested by non-EU regulatory authorities." seems to induce further confusion. Also adding a suggestion in "VIII. App 1.1.1.3. Registries", that registries may be useful to study the effectiveness of medicinal products in certain circumstances, seems to refer to PAES and provides no further clarity to methods for PASS. EFPIA acknowledges the need for PASS when the safety profile of a medicinal product needs to be confirmed (e.g. confirmation that a specific safety hazard is not linked to the product or that the frequency of a hazard is below a certain level) or when a risk minimisation measure needs to be assessed. However, it is our interpretation that the legislation did not intend to classify almost all post-authorisation studies as PASS. The overwhelming majority of clinical trials (both pre- and post-authorisation) include an element of monitoring of the safety profile of the medicinal product concerned – it is of our opinion this should not classify them as PASS. **Risk Management Plan** It was understood from prior presentations by the EMA e.g. on the RMP Information Day (30 June 2015) that there will be further clarification regarding the type of studies to be included in an EU RMP (category 1, 2, 3) and that PASS/Commitments required by non-EU regulators should not	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	be included in the EU RMP. This is welcomed, and consistency between the Modules would then become paramount. **PASS classification** In light of above comments that PASS should be limited to studies aimed at addressing important risks, missing information or effectiveness of risk minimization as defined in the EU RMP and no longer requiring that Cat 4 studies are listed in the EU RMP, we believe this category should (if judged to be still useful) be better defined. Indeed, a very broad variety of studies "may provide safety information of less significance" and all of them should in general not be classified as PASS. **Non-EU requirements/studies** It is important to confirm that full transparency with regard to studies being conducted by MAH will be maintained since a full list of studies will be included in the PBRER. In addition, the fact that an MAH may already be planning to conduct a safety study does not prevent EU regulators from requiring the study. However, studies should not automatically become required in EU simply because they are required outside EU. Any new safety findings that might arise from any post-authorisation study not formally classified as a PASS would, depending on the clinical significance of the finding, either be notified promptly to the EU (N)CA (e.g. if the risk-benefit profile were impacted) and/or included in the PSUR/PBRER as appropriate. **Other** EFPIA is seeking further clarification if non EU PASS and non-interventional PASS need to have EU product registration (e.g. in section VIII.B.3 and other sections in the document where it states all PASS). For the management and reporting of adverse events a	

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	requirement has been added that only the appropriate level of the MedDRA classification should be used. Since MedDRA is not the universal dictionary used in all post-authorization safety studies, a MedDRA translation would need to be included in protocols that utilize data sources with alternative coding e.g. read codes or ICD codes and mapping to MedDRA can be challenging and doesn't add value in all circumstances. EFPIA has noticed that throughout the text the role and function of 'CMDh' has been replaced by 'member states'. The rationale for this change is not fully understood. We would request further clarification on the role of CMDh. EFPIA suggests to consider reference to the Clinical Trial Regulation which will become applicable shortly after the anticipated coming into effect date of this module revision. We proposed ensuring consistency with regard to the definitions provided in Article 2 of Regulation (EU) No 536/2014 which refers to clinical studies, including clinical trials, low intervention clinical trials and non-interventional 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')*	Outcome *(To be completed by the Agency)*
68-71		**Comment:** GVP Module VIII should be amended to provide an explanation of the term "safety hazard" clarifying that, for the purposes of PASS, the term "safety hazard" relates to important risks and missing information listed in the safety specification of the EU-RMP. In addition, further clarification should be provided on the status of post-authorisation studies imposed by non-EU CA. **Proposed change (if any):** The inclusion of the following statement in *Section VIII.A Introduction* - immediately after paragraph 1 (after line 71) which defines a PASS: For the purposes of PASS, the term "safety hazard" relates to an important risk or missing information listed in the safety specification of the EU RMP.	
70-71		**Comment:** It would be helpful to have alignment of information provided in the GVP Modules. According to GVP Module XVI (p. 11), studies designed to assess the effectiveness of risk minimization measures are to be classified as PASS depending on the indicators they evaluate: '*The legislation defines "Any study ….measuring the effectiveness of risk management measures" as a post-authorisation safety study [DIR Art 1 (15)]. Therefore, if a study is conducted to assess behavioural or safety outcome*	

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		indicators the detailed guidance for conducting a post-authorisation safety study, which is provided in Module VIII, should be followed. Such guidance does not apply to the measurement of simple process markers (e.g. distribution of the tools reaching the target population)' In addition, the PASS status of studies assessing knowledge (a process indicator) should be clarified. **Proposed change**: *A post-authorisation safety study (PASS) is defined in Directive 2001/83/EC (DIR) Art 1(15) as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures <u>by assessing behavioural or safety outcome indicators</u>.*	
72-73		**Comment**: Suggest consistency with Article 2 of the new clinical trial regulation which refers to clinical studies, consisting of clinical trials, low intervention clinical trials and non-interventional studies **Proposed change:** Alignment of the classification of clinical studies as above.	
72-89		**Comment:** The MAH welcomes the clarification of the link between the legislation on non-interventional PASS and the categories 1-4 of non-interventional PASS in GVP Module V.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		However, it is important to clarify that not all categories 1-4 PV activities in an EU-RMP may qualify as PASS. For example, a phase 3 clinical trial may be considered by the MAH as required in the EU-RMP to further investigate a safety concern (category 3); however, the phase 3 clinical trial would not qualify as a PASS according to the definition in this GVP Module. **Proposed change (if any):** Add a clarification statement that not all categories 1-4 PV activities in an EU-RMP should be considered as PASS, and consider to citing the example provided.	
75		**Comment:** It will be helpful to clarify that a "competent authority" refers to an EU competent authority. **Proposed change (if any):** Amend text to state "imposed by an EU competent authority."	
74-77		**Comment**: Would be useful if the information is already added here that PASS conducted by a third party on behalf of the MAH are in scope as well (as mentioned in lines 129-130) **Proposed change (if any):** *"A non-interventional PASS may be initiated, managed or financed by a marketing authorisation holder voluntarily or pursuant to an obligation imposed by a competent authority [DIR Art 107m(1), 75 Regulation (EC) No 726/2004 (REG) Art 28b] including also studies conducted by a third party on behalf of the marketing authorisation holder."*	
74-89		**Comment**: The clarity of this paragraph would be enhanced with the use	

<table>
<tr><th>Line number(s) of the relevant text
(e.g. Lines 20-23)</th><th>Stakeholder number
(To be completed by the Agency)</th><th>Comment and rationale; proposed changes
(If changes to the wording are suggested, they should be highlighted using 'track changes')</th><th>Outcome
(To be completed by the Agency)</th></tr>
<tr><td></td><td></td><td>of a table listing the actual provisions of the legislation in a tabular form for each type of PASS by category. This should make clear what is imposed by law for each category, vs. what is recommended or may be imposed at NCA's level.

Proposed change:
Insert table

<table><tr><th></th><th>Category 1</th><th>Category 2</th><th>Category 3</th><th>Category 4</th></tr><tr><td>Provisions of Art 107m</td><td></td><td></td><td></td><td></td></tr><tr><td>Provisions of Art 107n</td><td></td><td></td><td></td><td></td></tr><tr><td>Provisions of Art 107o</td><td></td><td></td><td></td><td></td></tr><tr><td>Provisions of Art 107p</td><td></td><td></td><td></td><td></td></tr><tr><td>Provisions of Art 107q</td><td></td><td></td><td></td><td></td></tr></table></td><td></td></tr>
<tr><td>86</td><td></td><td>Comment:
This information refers to GVP Module V and category 4 studies which we understand will not be included in the future RMP template. This is welcomed, and consistency between the Modules is to be ensured.

Define Category 4 studies in Module V but if the EU RMP template will not include category 4 then this should be made very clear in the PASS guideline.</td><td></td></tr>
<tr><td>86-87</td><td></td><td>Comment:
Available safety data should always be collected, but this does not mean that all non-interventional studies are PASS. It should therefore be specified that only studies where safety is a primary endpoint, are regarded as PASS in this context.

Proposed change (if any):
those that may provide safety information of less significance (category 4 of studies of GVP Module V) <u>and where safety is a primary endpoint of the study</u></td><td></td></tr>
</table>

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120-128		**Comment:** Despite the current revision it is still unclear which requirements would be applied to PASS performed inside the EU and which apply to PASS performed outside the EU. For example, clarity is requested as to whether VIII.B of the guidance applies to non-interventional PASS requested by a non-EU HA. **Proposed change (if any):** Add further clarification to text, for example as follows: *This guidance ~~should~~ also ~~be used for~~ applies to studies conducted outside the EU, but only those studies which have been imposed or required by an EU competent authority (categories 1, 2 and 3 of studies defined in GVP Module V)."*	
126		**Comment:** *"A distinction is made in the text between situations where the provision of the guidance represents a legal requirement or a recommendation."* Suggest for completeness to also specify here that this distinction between legal requirement or recommendation should also consider country-specific legislation. **Proposed change (if any):** *"A distinction is made in the text between situations where the provision of the guidance represents a legal requirement or a recommendation. Country-specific legislation should also be considered."*	
141		**Comment**: As stated in line 72-73, this module concerns '*PASS which are clinical trials or non-interventional studies,*	

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		with a main focus on non-interventional PASS'. However, it is seems that the terminology defined in lines 141-155 only applies to non-interventional PASS studies. It is recommended to clarify that terminology defined in line 141-155 applies to non-interventional PASS only. **Proposed change**: *VIII.A.1.Terminology <u>for non-interventional PASS</u>*	
157-171		**Comment**: Section B.1. Principles is proposed to be amended to read: **Proposed change (if any):** *VIII.B.1. Principles* In accordance with DIR Art 1(15), a post-authorisation study should be classified as a PASS when the ~~main aim for initiating the study includes any of the following objectives:~~ <u>study is designed to investigate important risks, missing information or effectiveness of risk minimization, listed in the EU RMP.</u> • ~~to quantify potential or identified risks, e.g. to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a nonexposed population or a population exposed to another drug or class of drugs, and investigate risk factors and effect modifiers;~~ • ~~□to evaluate risks of a medicinal product used in patient populations forwhich safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment);~~ • ~~to evaluate the risks of a medicinal product after long-term use;~~ • ~~to provide evidence about the absence of risks;~~ • ~~to assess patterns of drug utilisation that add knowledge on the safety of the medicinal product (e.g. indication, dosage,~~	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		~~co-medication, medication errors);~~ • ~~to measure the effectiveness of a risk minimisation activity.~~ A study designed to investigate efficacy, cost-effectiveness or quality of life should not be classified as PASS. Studies conducted outside the EU and not intended to investigate a safety hazard, whether or not imposed by a non-EU regulatory authority, are also excluded from the definition of PASS.	
212-216		**Comment:** Clarification is requested regarding which studies should be registered in the EU PAS register, specifically with regards to the following: • applies to both imposed and voluntary PASS • applies to PASS requested by any HA (EU and non-EU) • applies only to non-interventional PASS Make clear that this is only for studies that meet the definition of a PASS as defined in Directive 2001/83/EC Article 1(15), and not the wider scope of non-interventional post authorisation studies. Also make it clear that this applies only to studies that involve a product authorised in the EU. **Proposed change (if any):** Amend text to clarify, as follows: *"In order to support transparency on non-interventional PASS and to facilitate exchange of pharmacovigilance information between the Agency, Member States and marketing authorisation holders, the marketing authorisation holder should make study information available in the EU electronic register of post-authorisation studies (EU PAS Register) maintained by the Agency and accessible through the European medicines web-portal. Registration in the EU PAS Register ~~also applies to studies conducted outside the EU, including non-interventional studies requested by non-EU~~*	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		~~regulatory authorities~~ applies to studies meeting the definition of a PASS (DIR Art 1(15) and VIII.B.3 principles) and are either: • *conducted in the EU (both imposed and voluntary), or* • *requested by any HA (EU and non-EU) including studies conducted outside the EU. "* *PASS which do not involve a product authorised in the EU do not need to be registered in the EU PAS Register.*	
217-218		Comment: *"Registration in the EU-PAS register also applies to studies conducted outside the EU, including non-interventional studies requested by non-EU regulatory authorities".* Please consider that in some (non-EU) countries, PASS are being requested, which may not follow the scientific and procedural guidance provided in this GVP Module. Further clarification on how to address these studies (i.e. whether these should be registered on the EU-PAS register) would be appreciated.	
218-219		**Comment:** *"The study protocol should be entered prior to the start of data collection."* This is practically not always possible, especially not in case of a voluntary PASS. One example would be a voluntary PASS that was already ongoing prior to July 2012 cut-off date, or prior to the safety concern being discussed.	

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		Another example would be a FDC development program for which an RMP mentions a risk that is addressed by a study that is conducted with one of the single agents, but for which the single agent RMP does not mention the risk. The study proposed at the time of the FDC RMP negotiation could in that case be already ongoing. **Proposed change (if any):** Amend text to allow for scenarios when entry of the study protocol prior to the start of data collection is not possible.	
219-221		**Comment:** *"the final study report should be entered in the register (preferably within two weeks after their finalisation)."* There is some concern with meeting a two week timeframe and we would propose extending this for better feasibility. **Proposed change (if any):** Amend text as follows: *"the final study report should be entered in the register (preferably within two weeks after their finalization <u>or within a timely manner where this is not feasible</u>)."*	
227-228		**Comment:** *"… a study protocol with redactions made by the marketing authorisation holder may be entered into the register prior to the start of data collection".* We would like to raise the concern that even knowledge of the study could bias the outcome of the study, particularly when PASS are performed to measure the effectiveness of risk minimisation activities.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
244-245		**Comment:** It should be reminded that the non-interventional PASS conducted pursuant to obligations imposed by a competent authority are supervised and assessed by the PRAC, or national competent authority of a single Member State. **Proposed change (if any):** For *non-interventional PASS initiated by the marketing authorisation holder pursuant to an obligation, which are supervised and assessed by the PRAC or a national competent authority of a single Member State, see modalities in VIII.C.2. for the submission of the study protocol.*	
246-247		**Comment:** GVP Module VIII Addendum I covers PASS that are voluntary, and not just those that are pursuant to an obligation. Therefore, "For these studies,….." may be unclear. **Proposed change (if any):** Amend to *~~"For these studies, r~~ Requirements for submission of the study protocol for centrally and nationally authorised products are specified in GVP Module VIII Addendum I."*	
248-250		**Comment:** The text here has not been revised, therefore a discrepancy exists between the wording in GVP I.C.1.3 (*'being involved in the review and sign-off of protocols of post-authorisation safety studies conducted in the EU or pursuant to a risk management plan agreed in the EU'*) and here in GVP VIII.B.3 (*'the qualified person responsible for pharmacovigilance (QPPV) or his/her delegate (see GVP Module I) should be involved in the review and sign-off of*	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		study protocols conducted in the EU'). **Proposed change (if any):** Align the wording in the two GVP Modules, as appropriate. For example, amend the text in GVP Module VIII as follows: *"In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) or his/her delegate (see GVP Module I) should be involved in the review and sign-off of study protocols conducted in the EU or pursuant to a risk management plan agreed in the EU."*	
342, 611		**Comment:** The term 'Benefit-Risk' is used in these lines, but 'Risk-Benefit' is used elsewhere. **Proposed change (if any):** Use the same term for 'Benefit-Risk' throughout the document for consistency.	
346-347 352-355		**Comment:** Since MedDRA is not the universal dictionary used in all post-authorization safety studies, a MedDRA translation would need to be included in protocols that utilize data sources with alternative coding e.g. read codes or ICD codes and mapping to MedDRA can be challenging and doesn't add value in all circumstances. For example: 1) Osteosarcoma ICD-O-3 diagnosis code 9184/3	

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		Osteosarcoma in Paget's disease of Bone would translate in MedDRA as Preferred term Osteosarcoma. In this case MedDRA does not provide the granularity required to describe the protocol defined AE of interest. 2) In Nordic countries, coding is done as per ICD10 at the registry level. Subsequent use of the MedDRA classification in such cases may invoke inconsistencies between the reporting using ICD10 and MedDRA thus at the case level, there may be a difference between the reports submitted to agencies and descriptions of reports within later publications. **Proposed change (if any):** *… using the appropriate level of the MedDRA classification when utilised …*	
356-358		**Comment:** It would be helpful to mention that even if the reporting of suspected adverse reactions is not required in case of secondary use of data all adverse events still have to be collected. **Proposed change (if any):** *"…for which all adverse events must be collected but the reporting of suspected adverse reactions……*	
409		**Comment:** The section numbering appears to need updating here. **Proposed change:** VIII.B.6.4.3.1 (rather than VIII.B.6.4.1 Progress Reports)	
446		**Comment:** The weblink of EU PAS Register is to be more emphasized.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any): *If the study has been registered in the EU PAS Register, the final study report should mention on the title page "EU PAS Register No:" with the registration number and the weblink to the study record.*	
580-583 587-590		**Comment**: A statement has been added on both line 583 and 589-590 to specify that: *"This provision should be applied for all PASS."* The addition of this statement creates some confusion as it seems to conflict with the first sentence of the corresponding paragraphs, until the reader realises the difference between the 'shall' and the 'should'. As this confusion is linked to the provisions imposed through the legislation, it is recommended that this is clarified (see also comment on lines 74-89 recommending the addition of a table clarifying the legislative provisions)	
592-599		**Comment:** It should be helpful to get more explicit guidelines on requirements for RMP updates related to study conduct. A reference to module V.C.3. Situations when a risk management plan should be submitted? should be provided and this section should be updated if finalized protocols may be submitted as part of RMP update.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any): • Add a sentence Line 594: *Situations of submission of risk management plan update are detailed in module V.C.3.* • Additionally, the last sentence (line 598-599) should be moved to the end of the first sentence (line 594).	
596-598		**Comment**: This paragraph mentions that finalised protocols should be included in RMP annex 6. It should be clarified whether e.g. the concept sheet of a planned PASS be included in Annex 6 until the final protocol is available.	
598-599		**Comment**: It should be clarified that studies that assess the effectiveness of additional risk minimization measures but do not qualify as a Post-authorization safety study (PASS) do not need to be described in the RMP. This is the case for studies that are aimed to evaluate educational materials (additional risk minimization measure) effectiveness based on physicians' knowledge on the risks associated with a specific drug. GVP Module XVI considers assessing clinical knowledge as a process indicator to evaluate additional risk minimization measures, although only studies conducted to assess behavioural or safety outcome indicators are qualified as PASS. Studies that evaluate knowledge are not discussed when describing what a PASS is. (see also comment on line 70-71)	

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632-639		**Comment:** Allign body text with header regarding *emerging safety concerns* in line 635/636 to make it clearer. **Proposed change (if any):** *After the granting of the marketing authorisation, the Agency or a national competent authority, where applicable, may impose on the marketing authorisation holder an obligation to conduct a post-authorisation safety study if there are emerging safety concerns about the risk of the authorised medicinal product [REG Art 10a, DIR Art 22a].*	
640-653		**Comment:** For joint PASS, it is not clear which of the MAH's should have their QPPV sign-off the protocol. Would this be just the innovator's QPPV for a generic product? Could there be a situation in which sign-off by more than one MAH's QPPV would be required. **Proposed change (if any):** For joint PASS, clarify which MAH's QPPV would need to sign-off the protocol, and indicate in which situations (if any) there would be a need for sign-off by more than one MAH's QPPV.	
655-659		**Comment:** In lines 658/659 it is indicated: *The national competent authority or the Agency shall specify a time limit for the provision of these observations.* It seems that time limit is 30 days as mentioned in line 655. These two sentences create confusion. **Proposed change (if any):** If this is the correct understanding, please align the sentences	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		for clarity.	
656		**Comment:** The addition of : "*after the granting of a marketing authorisation*" brings confusion as it could be understood as if the possibility of a written observation is only possible for obligations imposed through an initial marketing authorisation. However, the legislation REG Art 10a(2) and DIR Art 22a(2) is not specific to initial marketing authorisations: written observations in response to the imposition of an obligation are possible regardless of the procedure that drove the obligation i.e. following initial marketing authorisation or following any post-MA procedures. Therefore, the guideline should be kept as initially written for clarity sake. **Proposed change (if any):** Within 30 days of receipt of the written notification of an obligation imposed ~~after the granting of a marketing authorisation~~, the marketing authorisation holder may request the opportunity to present written observations in response to the imposition of the obligation [REG Art 10a(2), DIR Art 22a(2)].	
681-736		**Comment:** Would it be helpful to emphasise the requirements for ICSR management as outlined for non-interventional studies in GVP Module VI by cross-reference? **Proposed change:** Collection of adverse event/adverse reaction information should follow the requirements outlined in VI.C.1.2.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
756		**Comment:** It would be useful to understand the rationale in extending the timeline for the PRAC or NCA to provide their assessment to MAHs from 30 to 60 calendar days. As this information is critical to MAH, we propose to keep this as **30** days. **Proposed change:** The national competent authority or the PRAC will provide the marketing authorisation holder with a letter of endorsement or objection to the protocol amendment within ~~60~~ 30 days of submission.	
758-760		**Comment:** Please clarify that the assessment applies only if the studies in conducted in one MS. **Proposed change(if any):** "*Where the study protocol for a nationally authorised product through the mutual recognition or the decentralised procedure is assessed by a national competent authority because the study is only conducted in this single Member State, this national competent authority is invited to share its assessment with the other concerned Member States.*"	
780-781		**Comment:** Please make it clearer that chapter VIII.C.3 applies for non-imposed (voluntary) PASS. And if this chapter deals with the implementation of a PRAC recommendation as a result of the process described in chapter C.2.1, please make this clearer. For example by changing the section number into "C.2.4"	

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')*	Outcome *(To be completed by the Agency)*
794-795		**Comment:** Mutual recognition procedure or decentralised procedure are not specified in this sentence. **Proposed change:** change sentence accordingly for clarity	
886-891		**Comment**: Is this sentence aiming at PAES? If so, suggest not to include it in the absence of a wider discussion on PAES to provide important context, in particular the omission of detail relating to ongoing discussions about PAES and the need for randomization in groups in real life practice to avoid channelling bias **Proposed change**: Suggest clarify the scope of the detail within the 'Registries' section.	
995		**Comment:** 'Pragmatic trial' is a term used inconsistently between documents. **Proposed change**: Please provide a more appropriate and clearer definition of pragmatic trial	
1010		**Comment:** Please provide further guidance for when a drug utilization study is classed as a PASS.	

Please add more rows if needed.

ANNEX – ADDITIONAL COMMENTS

It has been noted that only selected sections were within the scope of current public consultation. However, EFPIA would like to raise additional comments to consideration by EMA, which might improve consistency and/or the understanding of the overall text for various readership / stakeholders.

Stakeholder number *(To be completed by the Agency)*	General comment (if any)		Outcome (if applicable) *(To be completed by the Agency)*
General		**Comment:** We welcome that this revised version of this guideline includes guidance that provides for flexibility of report structure and flow for results from multi-database studies, e.g., for multi-database studies that do not intend to present pooled results, it would improve readability of the report to maintain descriptive, outcome & main results, and other analyses sections together in one Results chapter per database.	
General		**Editorial comment:** Replace 'participants' with 'subjects' throughout document	
90-92		**Comment**: Suggest including a reference to the new clinical trial regulation definition which will become applicable shortly after the expected coming into effect date of the module revision	
93-94		**Comment:** This may not apply to DUS evaluating off-label use.	
93-96		**Comment:** The language concerning PASS non-interventional studies	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)		Outcome (if applicable) *(To be completed by the Agency)*
		should apply to all medicines and not just only to prescription medication. If non-prescription drugs are out of scope, it should be mentioned in the document. **Proposed change (if any):** Amend text as follows: "the medicinal product is ~~prescribed~~ administered in the usual manner…" '…and the ~~prescription~~ administration of the medicine is clearly separated….'	
169		**Comment:** Please provide further guidance for when a drug utilization study is classified as a PASS.	
183		**Comment:** A revision to the GPP guidelines is pending release. Suggest confirming that the document location information/link at reference 4 will remain accurate on release of the revised GPP guidelines to ensure the update to GVP VIII will remain up to date in this regard	
268-278		**Comment:** the suggested sub-sections for the abstract are not aligned with the respective section in the Protocol, in particular: • Sub-section 'Population' is inconsistent with the respective Section in the protocol. • The abstract should also address major limitations of	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)		Outcome (if applicable) *(To be completed by the Agency)*
		the study. **Proposed change:** • Align with study protocol (see comment regarding lines 300-305) • Insert sub-section 'Limitations of the research methods' after 'Data analysis' sub-section.	
300-305		**Comment:** 'Setting' section in protocol includes description of subjects; this is not the case in the study report **Proposed change:** Separate section headings for Setting and Subjects in the study protocol (to be aligned with Study Report) (see lines 473-478)	
318-320		**Comment:** 'Study size' section would better fit after the primary analysis has been specified in section 'Data analysis'. Guidance might be added that the justification of the study size should be based on the primary analysis (see also comment on lines 323-327).	
323-327		**Comment:** The primary analysis or main statistical analyses should be clearly identified in the 'Data analysis' section. Subgroup analyses and secondary analyses should be added to the list	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)		Outcome (if applicable) *(To be completed by the Agency)*
		of analyses to be described.	
458, 286		**Comment:** No clear definition of 'interim report' v 'progress report' **Proposed change (if any):** Include a definition or explanation of 'interim report' v 'progress report'.	
488		**Comment:** A section for 'Bias' (incl. confounding) in the Research Methods of the report is superfluous, as this topic is already discussed upfront in the study protocol's 'Limitations' section. Furthermore, a separate section for this topic in the Research Methods of the study report is redundant within this document because bias & confounding (and explanation of methods to minimize/control for these) is to be discussed in depth in the Discussion section of the report. **Proposed change:** Remove section 'Bias' from the Research Methods section of the study report. Efforts to assess and address potential sources of bias and confounding can be described in the Statistical methods section.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)		Outcome (if applicable) *(To be completed by the Agency)*
508		**Comment:** Sub-section heading 'Participants' in Results section of study report is inconsistent (i.e., use of consistent terminology throughout protocol and report). **Proposed change:** Change Results sub-section 'Participants' to 'Subjects' in study report [see also 2nd General Comment above]	
513, 517		**Comment:** Using the word 'data' is not appropriate, it should be replaced by 'results'. **Proposed change**: Change 'data' to 'results'	
523-524		**Comment:** primary data collection should be specified in sentence "summary of all adverse events/adverse reactions reported in the study, in line with requirements described in GVP Module VI." **Proposed change (if any):** add primary data collection to make it distinct from secondary use of data added thereafter.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)		Outcome (if applicable) *(To be completed by the Agency)*
530-540		**Comment:** Separate sub-sections for limitations, interpretation and generalisability reduce readability of the discussion section. A structure commonly used in scientific publications in which the discussion of results directly follows the summary of key results and a separate discussion of limitations and generalisability directly precedes the conclusions is much better to understand. **Proposed change:** • Remove sub-section for key results, limitations, interpretation and generalisability. • Alternatively, exchange sub-sections Interpretation and Limitations so that Interpretation (i.e. discussion of the results) directly follows the key results. • A sub-section for Conclusions might be added.	
Lines 585-590		**Comment:** It would be helpful to provide guidance for the required duration for keeping analytical dataset and statistical programmes that are used for generating the data included in the final study report for auditing and inspection purpose **Proposed change (if any):** Provide duration. *For PASS imposed as an obligation, the marketing*	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)		Outcome (if applicable) *(To be completed by the Agency)*
		authorisation holder shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection [IR Art 36]; for a period of at least 3 years after completion of the study. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s)	
675-680		**Comment:** Consider adding that this applies to Category 1 and 2 additional PV activities in the EU-RMP. **Proposed change (if any):** Amend text as follows: *'Non-interventional PASS conducted pursuant to obligations imposed by a competent authority (Category 1 and 2 additional PV activities in the EU-RMP) are supervised and assessed by the PRAC….'*	
725-731		**Comment:** When reading this section, there is a break and/or missing text with regard to the content from 1st sentence to the 2nd sentence concerning the waiver, see text copied below: When the PRAC is involved in the oversight of the study, the marketing authorisation holder shall submit the final study report to the PRAC and to the Agency. When the PRAC is	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)		Outcome (if applicable) *(To be completed by the Agency)*
		responsible for regulatory supervision of the PASS, the marketing authorisation holder should request the waiver in writing to the Agency at least three months before the due date for the submission of the report. The request should include a justification for the waiver. The request should be assessed by the PRAC rapporteur and granted or rejected by the PRAC on the basis of the justification and timeline submitted by the marketing authorisation holder. **Proposed change (if any):** Please adapt wording with missing text part on waiver.	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 October 2015

Submission of comments on GVP Module VIII – Post-authorisation safety studies (Rev 2) (EMA/813938/2011)

Comments from:

Name of organisation or individual
EGA – European Generic and Biosimilar medicines Association [redacted]

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

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

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An agency of the European Union

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The EGA welcomes this opportunity to comment the new revision of the *GVP Module VIII – Post-authorisation safety studies* and as well welcomes a further development of this module. Furthermore, EGA appreciates EMA's efforts to continuously improve guidance documents taking on-board not only stakeholders' experience, but as well challenges and needs. Availability of clear, up-to-date guidance documents is crucial for a smooth daily regulatory work. Therefore, we would very much appreciate not limiting public consultations to marked sections only, allowing inclusion of further clarification on e.g. different categories of PASS and the recommended setup of study protocols. A more transparent and unequivocal guidance is still what MAHs would very much appreciate.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 162		Comment: Term 'intervention' might lead to confusion since it is used in clinical trials. To avoid any misunderstanding it should be replaced by a more appropriate term. Proposed change (if any): -	
Lines 212-221		Comment: Registration in, and submission of documents into the EU PAS Registry is noted. Proposed change (if any): That the EU PAS Registry should be used as a portal for the submission of all study documents and be used for the further dissemination to Member States and PRAC members. Having the MAHs to submit documents to individual MS and each PRAC member is an inefficient use of MAHs resources	
Lines 594-599		Comment: It is not clearly stated as to how NIS-PASS should be described when a protocol and design are under development during the RMP preparation. In this case the protocol would not be available to be added to the RMP although the NIS-PASS should be already mentioned. Also, it should be clearly stated if the protocols which are provided in RMP annex 6 should be final proposed or final approved by the competent authority.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any): If draft/approved protocol is not available for the non-interventional PASS during the update of RMP, all relevant sections of RMP should be updated as appropriate and RMP annex 6 a note should be included that protocol is under preparation and it will be submitted to relevant health authority for approval before commenting the study. If study is being conducted during the update of RMP, all relevant sections/modules of the RMP should be amended to document the conduct of the study, including the safety specification, the pharmacovigilance plan, the risk minimisation plan and the summary of activities, as appropriate. Approved protocols for studies in the pharmacovigilance plan should be provided in RMP annex 6 until submission of the final study report to the competent authorities. Studies looking at the effectiveness of risk minimisation measures should be included in the pharmacovigilance plan as well as described in detail in the risk minimisation plan.	
Lines 609, 635		Comment: It is noted that a PASS can be imposed "…are concerns about the risk(s) of an authorised medicinal product." All medicinal products have risks and for those products with a RMP, these are presented as a summary of safety concerns. This wording implies that a PASS could be imposed for any of these. Proposed change (if any): The wording should be rephrased so	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		that a PASS is not imposed unless it is anticipated that the concern is significant and that a PASS would be expected to generate robust evidence to either confirm or refute the concern	
Lines 644-648		Comment: Proposal for a joint post-authorisation safety study (PASS) can hardly be achieved considering differences in size of pharmaceutical companies and their capabilities to perform specific PASS requirements. While a re-analysis of company owned data and sharing of the results with other companies is possible and has been performed already, agreement on common core elements for the joint protocol is not realistic. In addition, Agency would need to clearly commit to lead any such effort in order to increase the likelihood of success of joint PASS. Proposed change (if any): Requests to the marketing authorisation holders should contain the justification for the request of a joint study ~~and may include core elements for the study protocol~~. Upon request from the marketing authorisation holders, the national competent authority or the Agency ~~may provide suggestions for a joint study proposal and~~ will facilitate agreement in developing a joint ~~protocol~~ approach.	
Line 648		Comment: 'If a joint protocol is not voluntarily agreed…' This sentence was deleted. However, the guidelines should address the situation when the MAH choose to opt out of the joint 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')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	
Lines 737-763		Comment: There is no apparent guidance to the PRAC and NCAs on the need for them to give clear and unequivocal guidance to MAHs on a PASS. Experience to date is that the time taken from initial notification of the need for a PASS to approval of the study protocols is too long. Part of the reason for this is a lack of clarity on the scope of the proposed PASS. Proposed change (if any): EMA to include a clause to require the MS and PRAC to give clear and unequivocal guidance on the scope of a PASS.	
Line 982		Comment: women of childbearing potential are all women aged 18-45. This subpopulation is neither small in size nor commonly excluded from clinical trials. Proposed change (if any): replace “women of childbearing potential” with “pregnant women”	

Please add more rows if needed.

October 9th 2015

Submission of comments on GVP Module VIII – Post-authorisation safety studies (Rev 2) (EMA/813938/2011)

Comments from:

EUCROF (European CRO Federation) joint collaboration of Late Phase Working Group, Clinical Trial Legislation Working Group, Pharmaco Vigilance Working Group

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The revision 2 of the module is more harmonized with specifications applicable to non-interventional PASS reported in Module V and Module VI. However, provisions applicable to Cat. III PASS protocols, in terms of PRAC oversight on protocol and on study progresses, might require further description. Joint PASS protocols are an area of endless discussions and difficult consultations in order to agree on a single protocol(reference is made to Lines 640-653). Since this is a typical area of duplicate effort and costs for both MAHs and the Agency it is suggested a revision that aims to minimize effort, reduces cost and enhances patient safety.	

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)*
106		Comment: What is the purpose of adding the word “collection” in the sentence? In these studies, interviews, questionnaires and collection of blood samples may be performed as part of normal clinical practice. Is it a clarification (e.g. to include the concept of using blood samples drawn as part of the routine clinical practice) or just a linguistic correction?	
216		Comment: It is not clear when a study conducted outside EU should be register in the EU PAS Register. Should it be done when the MAH is submitting a first central market authorisation or a renewal? Where is the legal grounds for registration when the study is done totally outside the EU? One reason could be that it is an EU imposed study. But that is not mentioned in lines 216-218 (although it is in lines 121 – 123).	
244		Comment: It may be useful to clarify also provision for PRAC protocol oversight for Cat. III study. It is reported that PRAC oversight is within the RMP, but the process is not clearly described. What happens if the MAH submit a Cat. III study protocol to PRAC? Do provisions applicable for Cat. I-II become applicable also to the Cat. III evaluated protocol? Proposed change (if any): please add additional 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')*	Outcome *(To be completed by the Agency)*
356		Comment: In Module VI footnote 24 it is defined that in case of study design combining primary and secondary data collection, the adverse events/reactions reporting should follow the rules defined for primary data collection. It could be useful to report this specification also in Module VIII. Proposed change (if any):please report the text of Module VI footnote 24, after line number 358.	
673-674		Comment: If these lines are deleted, there is no reference to this case in the document. There must be a clear statement as to what should a MAH do in this case: develop a new RMP or not.	
760		Comment: What does “invited” mean in this case? It might be advisable to use a more precise word	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5th October 2015

Submission of comments on GVP Module VIII – Post-authorisation safety studies (Rev 2) (EMA/813938/2011)

Comments from:

Name of organisation or individual
Gilead Sciences International Ltd.

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

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)*
124-125		Comment: the text '…requirements which are applicable to studies conducted pursuant to an obligation are recommended to all PASS'… It would be helpful to elaborate on 'all PASS' and state clearly that this includes those PASS that are conducted voluntarily by the MAH and clarify whether it also includes PASS, which are interventional clinical trials. Some of the recommended/required format for PASS protocols does not lend itself well to interventional trials and clarification or separation of NIS vs Clinical trials would be helpful. Proposed change (if any):	
154		Comment: when referencing the statistical analytical plan, it should be made clear that this is with regards to the planned analyses described in the protocol, where changes would be considered a substantial amendment. The supporting, extensive SAP, which is a separate document should not automatically be considered a substantial amendment, particularly as the SAP is often developed some time after the finalised protocol. Proposed change (if any): 'the statistical analytical plan as described in the study 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')*	Outcome *(To be completed by the Agency)*
212-218		Comment: text 'Registration in the EU PAS Register also applies to studies conducted outside the EU, including non-interventional studies requested by non-EU regulatory authorities.' In lines 122-123 it is stated that 'This guidance should also be used for studies conducted outside the EU which have been imposed or required by an EU competent authority (categories 1, 2 and 3 of studies defined in GVP Module V).' The text in 212-218 appears to require registration also of studies mandated by non-EU authorities, and appears to conflict with the earlier statement in 122-123 that guidance VIIIB applies to studies mandated by EU authorities, whether conducted within or outside the EU. It is further unclear whether the registration is expected for all PAS or only PASS, as the very beginning of the paragraph specifically refers to non-interventional PASS. Further clarification required also because currently we don't consider non-EU regulatory agency requirements for routine DUS/PMS studies as PASS e.g Japan PMS or Korea as examples as these are standard practice to perform. Proposed change (if any): Please could the text be clearer that those mandated for a specific safety concern or mandated beyond what is routine practice in a territory should be evaluated, and determined if a	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		PASS and managed accordingly	
583		Comment: The statement 'This provision should be applied for all PASS' is a bit confusing here, since the paragraph starts out referring to PASS imposed as an obligation. Proposed change (if any): Amend paragraph from Line 580 to state..."For all PASS, regardless of whether imposed as an obligation, the marketing authorisation holder shall ensure..."	
589		Comment: Same comment as above for Line 583 Proposed change (if any):	
596-598		Comment: Does this mean that RMP needs to be updated every time there is a protocol amendment? Proposed change (if any):	
620-621		Comment: This statement is unclear: "...the PRAC may adopt an advice with an assessment report...". Proposed change (if any): Please clarify	
630		Comment: Same comment as above for Line 620. Proposed change (if any): Please clarify	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
638		Comment: Same comment as above for Line 620. Proposed change (if any): Please clarify	
869-870		Comment: sentence 'More detailed information on adverse events from a large number of physicians and/or patients may be collected'… appears to be disconnected from the previous list of limitations of PEM studies and its purpose is not clear. Proposed change (if any): suggest to delete or link more clearly with the previous text in the paragraph – or start a new one and explain the purpose.	
952-956		Comment: text deleted – it is not clear why this text was removed and the question is whether the explanation on nested case-control studies should be retained. Proposed change (if any):	
1010-1013		Comment: suggest to add to the sentence the fact that DUS may be particularly useful for a first estimate of the level of public health concern arising from a possible risk associated with the use of a medicinal product – depending on the prescribing volume in a given population potentially at risk – for example in off-label prescribing Proposed change (if any):	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7th October 2015

Submission of comments on GVP Module VIII – Post-authorisation safety studies (Rev 2) (EMA/813938/2011)

Comments from:

Name of organisation or individual
Guild of Healthcare Pharmacists

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1. General comments

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

Bringing Post authorisation safety studies into line with clinical trials is a positive way forward and the clarification will be helpful.

It is probably safer to treat PASS as any other study to ensure that the full data set is reported.

Adding the link to the study record (line 446) will save time searching for the study record.

Section VIII.C.2 C gives a useful clarification of the roles and responsibilities of the marketing authorisation Holder.

2. Specific comments on text

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

Please add more rows if needed.

<Date of submission>

Submission of comments on 'GVP Module VIII – Post-authorisation safety studies (Rev 2)'

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 (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Overall, this revision of GVP Module VIII – Post-authorisation safety studies (rev 2), along with its accompanying addendum, is very comprehensive, clarifies previous guidance, and expands requirements for PASS related to medicinal products authorised for human use in the EU. We applaud the Agency for efforts to provide clear and comprehensive guidance. Further, we appreciate the opportunity to review this document and provide the following comments with the goal of improving, and thereby strengthening, GVP Module VIII. We provide separate comments on GVP VIII Addendum I (rev 2).	
	We suggest adding a summary of requirements and recommendations for voluntary PASS to complement those provided for imposed PASS.	
	Reference is made to Directive 2001/20/EC throughout, which we anticipate will be replaced by Regulation No 536/2014 sometime in 2016. Will GVP Module VIII be updated again with references to the new Regulation once it becomes effective?	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The requirements for the transmission of statistical analytical plans are added in Module VIII Addendum I Rev 2 Draft. We suggest referencing this in Module VIII (rev 2).	

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 106-107		Comment: We suggest further clarification of specimens, assessments, and follow-up that can be part of non-interventional study protocols. Proposed change: "In these studies, interviews, questionnaires, and ~~collection of blood~~ samples of blood, urine, cheek swabs may be ~~performed~~ collected as part of normal clinical practice and tested for research purposes; standardized follow-up generally consistent with normal clinical practice for the patient population may be included as well."	
Line 132		Comment: Please clarify that "persons" refers to "patients" as described in line 131. Proposed change: "… data previously collected from ~~persons~~ patients and healthcare …"	
Line 134-137		Comment: This paragraph refers to "Interventional" and "Non-interventional" PASS. Does interventional mean 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)*
		same as a clinical trial? Definitions should be consistent. Proposed change: Include definitions, as proposed for Lines 72-73.	
Lines 216-218		Comment: The statement, “Registration in the EU PAS Register also applies …,” implies that PASS criteria should be applied to non-interventional studies requested by non-EU regulatory authorities. If this is the intention, it is unclear how the EMA’s authority covers studies requested by non-EU regulatory authorities, especially for medicines that are not authorized in EU. Also, what is in scope for registration purposes, i.e., do patients have to be citizens of EU Member States? Will a study with all non-EU patients and, perhaps, requested by an ex-EU regulatory authority support a variation to the SmPC? Proposed change: Reconsider.	
Lines 313-14 and 368-69		Comment: We suggest linking the reference to pilot studies in the Data Sources section to the reference to feasibility analyses here. 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)*
		"Feasibility studies that are part of the research process should be described in the protocol, for example, a pilot evaluation of the study questionnaire(s) used for the first set of patients recruited into the study (see section 9.4, Data sources, above).	
Lines 340-358		Comment: Additional guidance and definitions are needed for studies based on secondary use of data. What is the definition of an valid adverse event in such studies? Will all non-MedDRA codes need to be converted to MedDRA? Proposed change: In GVP Module VI – Management and reporting of adverse reactions to medicinal products, clarify expectations regarding coding in in secondary use datasets.	
Line 389-399		Comment: The intent of the sentences relating to the risk-benefit balance is not clear. Greater clarity is needed re: which information and which studies should be considered for an Emerging Safety Issue vs routine reporting via the PSUR and RMP. 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)*
		"…to the Agency via email (P-PV-emerging-safety-issue@ema.europa.eu). Guidance for Emerging Safety Issues is provided in GVP Module IX – Signal management. Information affecting the risk-benefit …"	
Lines 423-424		Comment: The meaning of "safety findings" is unclear. This term should apply only to final study results. Proposed change: "Upon study completion, ~~s~~Safety findings should ~~also~~ be reported in the periodic safety update reports (PSURs) (see GVP Module VII) and the risk management plan (RMP) updates (see GVP Module V), where applicable."	
Line 692		Comment: "The marketing authorisation holder has the responsibility to ensure that the study is not a clinical trial,…" A PASS can also be designed as a clinical trial. It is not clear whether such a PASS would be reviewed by the National Competent Authority only or both the NCA and the PRAC. Proposed change: Clarify roles and responsibilities of the MAH and the EU Network regarding PASS oversight.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 831		Comment: The new text is a bit abrupt within the current paragraph. Proposed change: "… treated with a particular medicinal product through a risk management system. As an example, p~~P~~atients who fill a prescription for this product may …"	
Lines 834-835		Comment: We suggest providing some examples to illustrate "delayed effects", i.e., adverse events with long latency period (such as cancer). Proposed change: "However, some of the limitations of spontaneous reporting system~~s~~ still apply, especially when evaluating delayed effects. For example, adverse events that ordinarily have a lengthy time from exposure to onset, such as cancer, may not be readily detected via the spontaneous reporting system."	
Lines 881-882		Comment: We suggest providing some examples of existing databases, i.e., national cancer registries, inpatient/hospitalization, etc.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change: "… registries can be enriched with data on outcomes, confounding variables and effect modifiers obtained from a linkage to an existing external database, such as a national cancer registry."	
Lines 892-896		Comment: Given some confusion around registries and cohort studies (although a registry is a data collection infrastructure that enables implementation of various study designs, such as a cohort study, these two terms are frequently considered as synonymous). To further clarify, we suggest adding (in addition to the embedded case-control example,) an example of a cohort study embedded in a registry. Proposed change: "For example, a case-control study may be performed to compare the exposure to the medicinal product of cases of severe adverse reactions identified from the registry and of controls selected from either patients within the registry or from outside the registry. Likewise, a cohort study may be embedded in a registry."	
Lines 949-952		Comment: As currently written, these two sentences appear to be	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		redundant. Proposed change: "When the source population for the case-control study is a well-defined cohort or catchment area, it is then possible to select a random sample from it to form the control series. In these situations, because the sampling fractions of cases and controls are known, ~~. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known,~~ a case-control study may also provide the absolute incidence rate of the event. ~~When the source population for the case-control study is a well-defined cohort, it is then possible to select a random sample from it to form the control series."~~	
Lines 987-989		Comment: The additional text clarifies that data collection and monitoring should be minimally burdensome in a large simple trial. We suggest that this is also true for non-interventional studies involving primary data collection, where some additional and minimally burdensome data collection/monitoring are necessary for research purposes, e.g., standardization of outcome measurement. This needs clarification.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change: "A large simple trial is a specific form of clinical trial where large numbers of patients are randomised to treatment but data collection and monitoring ~~is~~ are kept to the minimum, consistent with the aims of the study to be a relatively low burden. Likewise, standardized follow-up generally consistent with normal clinical practice for the patient population may be included."	
Lines 995-996		Comment: The definition of pragmatic trials should be given, or it should be noted as a synonym for large simple trials. Proposed change: "Pragmatic trials are a kind of large simple trial~~s~~. As used in this context, the definition of a pragmatic trial is synonymous with a large simple trial."	
Minor		Comment: Consistent terminology would enhance clarity of the Module. For example, "benefit-risk" appears on Lines 342 and 611, whereas "risk-benefit" appears on Lines 42, 388, 390, 391, 394, 413, 532, and 990. Proposed change: Review the document for consistency in use of terminology.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*

08 October 2015

Submission of comments on GVP Module VIII – Post-authorisation safety studies (Rev 2) (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	Outcome *(To be completed by the Agency)*
	PHARMIG, the association of the Austrian pharmaceutical industry, welcomes the opportunity to comment on revision 2 of GVP Module VIII – Post-authorisation safety studies (EMA/813938/2011).	

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)*
73		It does not address non-clinical safety studies. Comment: Please clarify what type of studies fall under the definition of non-clinical safety studies? Proposed change (if any):	
644 - 653		~~Requests to the marketing authorisation holders should contain the justification for the request of a joint study and may include core elements for the study protocol. Upon request from the marketing authorisation holders, the national competent authority or the Agency may provide suggestions for a joint study 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 define, in consultation with the PRAC, either a common core protocol or key elements (for example, the study design, the study population and the definition of exposure and outcomes) which each marketing authorisation holder will have to implement in the study protocol to be submitted to the national~~	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		~~competent authority or the PRAC in accordance with DIR Art 107n(1).~~ Comment: Please explain why this abstract has been deleted? PASS is an additional risk minimisation measure and has to be seen in conjunction with the RMS. Proposed change (if any):	
867		…prescription event monitoring include substantial loss... Comment: Proposed change (if any): including	

Please add more rows if needed.

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SCIENCE MEDICINES HEALTH

09/10/2015

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP)- Module VIII- Post-authorisation safety studies (Rev 2)'

(EMA/813938/2011, Rev 2)

Comments from:

Name of organisation or individual
[redacted] on behalf of the REGenableMED consortium

Please find below the answer to the 'Guideline on good pharmacovigilance practices (GVP)- Module VIII- Post- authorisation safety studies (Rev 2)' by the REGenableMED consortium.

REGenableMED - REGenableMED is a United Kingdom Economic and Social Research Council (ESRC)-funded project (N°ES/L002779/1: http://www.york.ac.uk/satsu/regenablemed/). It brings together research team builds on work by social science experts based in Birmingham, Edinburgh, Sussex and York in the UK. It is coordinated by [redacted], Science and Technology Studies Unit at the University of York, UK. The project aims to examine the dynamics of innovation within the field of regenerative medicine. Using a mixed-methods social science approach, the project will undertake a detailed analysis of the interplay between business models, measures of clinical utility, patterns of regulatory oversight and clinical workflows within healthcare settings. The results of the research will inform strategies aimed at facilitating the responsible development of effective and useful regenerative medicine products and services.

All work packages of the project consider what we call the 'institutional readiness', i. e. the capacity and willingness of key pre-existing organisations and inter-organisational structures to adopt, respond

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to and utilise novel technologies, such as advanced therapy medicinal products as part of regenerative medicine. One work package led by [redacted], Centre for Global Health Policy, School of Global Studies, University of Sussex, the UK is dealing with the role of a range of intermediary agencies, patient groups and health insurance companies, in determining what can be called 'healthcare readiness' for the field, that is, how the field aligns with and can be embedded in existing practice and how far changes need to be made. As part of this work a regular survey of regulatory tools (including relevant linked public consultations) that influence the pathways through which the field develops is performed. The draft response has been prepared by [redacted], academic lawyer, [redacted], sociologist. A discussion between persons interested was then organised and the attached answer circulated to all project participants before submission.

The REGenableMED consortium is grateful to the European Medicines Agency to have been given the opportunity to contribute to this consultation.

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	All the partners of the REGenableMED project are aware of the existence of this draft Guideline. We welcome the opportunity to review this Guideline on good pharmacovigilance practices (GVP)- Module VIII- Post- authorisation safety studies (Rev 2)	

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)*
132		Comment: If there is a specific reason for using the word "persons" instead of "patients", could you please explain it? Otherwise, "patients" should replace the word "persons". Proposed change (if any): "those that make secondary use of data previously collected from ~~persons~~ patients and healthcare professionals"	
603		Comment: The sentence should not be deleted. See below line 664.	
664		Comment: The entire "Section VIII C. 3 Impact on the risk management system" has been deleted. It should be maintained as Regulation (EC) No 726/2004 and Directive 2001/83/EC include provisions for post authorisation safety studies to be a condition of the marketing authorisation in certain circumstances. Reference to Module V should be maintained while reference to Module VIII. B. 10 should be deleted. Proposed change (if any):	
871- 903		Comment: These developments on registries are particularly welcomed, as registries are keys to post- authorisation safety studies. Proposed change (if any):	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
885- 886		Comment: This sentence should be tempered, as registries can be key tools to demonstrate efficacy especially in the context of conditional marketing authorisation or where post-authorisation efficacy studies are required (ATMPs and Adaptive licensing pilot project). Proposed change (if any):	

Please add more rows if needed.

8 Oct 2015

Submission of comments on GVP Module VIII – Post-authorisation safety studies (Rev 2) (EMA/813938/2011)

Comments from:

Name of organisation or individual
SEC Associates, Inc.

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Thank you for the opportunity to address the changes in this draft. The guidance shouldn't state or imply that public posting of voluntary PASS by the MAH is required by EU law when it isn't in this case. The phrase "For these studies, **requirements** for submission of the … for centrally and nationally authorised products are specified in GVP Module VIII Addendum I" is repeated throughout, where "these studies" refers to both voluntary and obligatory PASS. Requirement typically means required by law. EU legislation does make distinctions between voluntary and obligatory PASS as to what is required by law. However, not everything in the Annex (Addendum I) is actually required by law – such as the MAH being required to publicly register PASS. But since the GVP says the requirements for submission are in the Annex, some careful rewording should be considered in both documents. As currently drafted, the Annex basically says it is a requirement (which means required by law, not recommended and not a suggestion) for voluntary PASS protocols, amendments, progress reports, final study reports and abstracts to be registered and publicly posted on the EU PAS register.	

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)*
127-128		Comment: The text states that “A distinction is made in the text between situations where the provision of the guidance represents a legal requirement or a recommendation.” However, the distinction seems to be lost when the phrase “For these studies, **requirements** for submission of the … for centrally and nationally authorised products are specified in GVP Module VIII Addendum I” is repeated throughout, where “these studies” refers to both voluntary and obligatory PASS. Requirement typically means required by law. Proposed change (if any): Re-evaluate the guidance and the annex for legal requirements vs recommendations. Submission and public posting by the MAH via the EU PAS Register is not required by law.	
212-216		Comment: This is an accurate statement, but it does not appear to be reflected in the rest of the document, nor in the Annex, relative to the other issues raised in our comments concerning the use of “required”. The text is repeated here for convenience: “In order to support transparency on non-interventional PASS and to facilitate exchange of pharmacovigilance information between the Agency, Member States and marketing authorisation holders, the marketing authorisation holder **should** make study information available in the EU electronic register of post-authorisation studies (EU	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		PAS Register) maintained by the Agency and accessible through the European medicines web-portal." Proposed change (if any):	
246-247		Comment: not everything specified in the Annex, such as submission and public posting by the MAH of study protocols for voluntary PASS via the EU PAS register, is required by law. In fact, submission to NCA is only on an "if requested" basis (and not via EU PAS). Proposed change (if any): For these studies, requirements and recommendations for submission of the study protocol for centrally and nationally authorised products are specified in GVP Module VIII Addendum I.	
384-384		Comment: public posting (and hence submission) by the MAH of study amendments for voluntary PASS via the EU PAS register is not required by law. Proposed change (if any): Requirements and recommendations for transmission of substantial amendments to the study protocol are specified in GVP Module VIII Addendum I.	
418-419		Comment: public posting (and hence submission) by the MAH of progress reports for voluntary PASS via the EU PAS register is not required by law.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Requirements and recommendations for transmission of progress reports are specified in GVP Module VIII Addendum I	
437-438		Comment: public posting (and hence submission) by the MAH of final study reports for voluntary PASS via the EU PAS register is not required by law. Submission to NCAs yes, but not via EU PAS register for public disclosure. Proposed change (if any): Requirements and recommendations for transmission of the final study report are specified in Module VIII Addendum I.	

Please add more rows if needed.