9 December 2016
EMA/847158/2016

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

GVP Module IX – Signal management (EMA/827661/2011 Rev.1)

The draft of this module was released for public consultation between 8 August 2016 and 14 October 2016. 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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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
The Association of the European Self-Medication Industry (AESGP)

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

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	AESGP has the following general comments: ▪ The anticipated date for the revised guideline to come into effect is Q1 2017. Consideration needs to be given that the effective date is aligned with the date when Marketing Authorisation Holders (MAHs) will be able to monitor and access data in EudraVigilance for signal detection, ▪ The introduction should clarify that the module is applicable for products with marketing authorisation in the EU in line with the quoted legislation in the introduction section (namely products in development are not in scope), ▪ The module describes the signal management process from the regulatory perspective and includes information on how MAHs should contribute to this process, which seems to be in the spirit of the legislation. The steps included in the module for European Medicines Agency (EMA), National Competent Authorities (NCAs) and MAHs could however be clearer and provide further guidance on some of the signal management steps required from MAHs or could acknowledge that MAH processes could be different, ▪ The draft module does not address the point that companies can have different signal management processes, which will run in parallel with the EU process. This should be acknowledged in the module. The conclusions of signal evaluations conducted by regulators and MAHs can potentially differ with MAHs initiating actions worldwide based on their conclusions. This could potentially lead to discrepant actions taken in the EU and the rest of the world. However, this could be addressed by ensuring clear timelines are applied in the EU process, so MAHs could make adjustments if needed in the timeframes of their signal management process. It would also be helpful is the changes vs. original version of Module IX (*in which all steps of signal management to be followed by any/all parties were clearly set out under IX.B.3 i.e. signal detection, validation, analysis and prioritisation, assessment,*

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	recommendation for action) were explained at the beginning. Currently in rev 1, it is not clear from the beginning that MAHs only carry out signal detection and signal validation (including resulting decision-making), and that CAs and PRAC are the only parties who carry out signal confirmation, analysis, assessment and recommendation. This only becomes clear in Table IX.1 on pages 10-11, and in Sections IX.C.4, IX.C.5 and IX.C.6. Also section IX.B.3 covers decisions that MAH could make in response to a signal, but does not mention communicating signals, and does not even cross-refer to the later section IX.C.3 where all the MAH options for communication are described. AESGP responses to the four questions on which the EMA seeks specific feedback by means of the public consultation: Question 1: ARE THE PROPOSED CRITERIA FOR ACCESS TO CASE NARRATIVES HELD IN EUDRAVIGILANCE BY MARKETING AUTHORISATION HOLDERS ACCEPTABLE (SEE IX.C.2.1)? The proposed criteria for access to case narratives held in EudraVigilance by MAHs are acceptable; assuming this refers to access to case narratives from other MAHs who have products with the same substance. Question 2: ARE THE RECOMMENDATIONS REGARDING THE FREQUENCY OF MONITORING OF EUDRAVIGILANCE DATA ACCEPTABLE (SEE IX.C.2.2)? The recommendations regarding the frequency of monitoring of EudraVigilance data are acceptable. Question 3: ARE THE PROPOSED TIMELINES AND MODALITIES FOR COMMUNICATION OF EMERGING SAFETY ISSUES AND VALIDATED SIGNALS BY MARKETING AUTHORISATION HOLDERS CLEAR AND ACCEPTABLE (SEE IX.C.3)? For communication of emerging safety issues, 2 working days is acceptable *from when the company has established that it is an emerging safety issue (i.e. valid)*. For validated signals, 3 months is acceptable from when the CCSI (reference safety information) has been updated and finalized in response to the signal, but may be insufficient time to incorporate the update and finalization of the CCSI as well as submission of

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	safety variations; therefore propose 4 months in total. Proposed timelines and modalities for PSUR and Standalone signal notification are acceptable.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
112		**Comment**: The EU signal management process described is that of the EMA and NCAs, it should be noted that MAHs processed may differ. **Proposed change** (if any): The EU signal management process includes the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment and recommendation for action [I Art 21(1)]. MAHs may have an alternate process but should encompass the general principles of the EU signal management process.
117 - 121		**Comment**: The signal validation definition no longer refers to the existence of a potentially causal association. ▪ Is this deliberate? ▪ Is the GVP Annex I definitions to be revised accordingly? ▪ Causality does seem to be included in Section IX.B.3 Lines 192-195
118 - 119		**Comment**: The definition of signal validation does not tie up with going straight to a variation in line 400 (if validation is to justify further analysis of the signal, there would not be enough information to submit a variation?) **Proposed change** (if any): Detailed guidance on the term signal validation is needed.
122 - 130		**Comment**: Any step from signal confirmation onwards appears to be a step for EMA and NCAs but not for MAH. Therefore, it is quite confusing to know what is expected of the MAH. There is no recognition that MAHs go through the signal detection and evaluation process on a global basis, and to contribute to the overall evaluation done by the MAH. **Proposed change** (if any): To accommodate for the evaluation process completed by MAHs and feed into the Pharmacovigilance Risk Assessment Committee (PRAC) assessment the conclusions of the MAH.
167 - 172		**Comment**: Further clarification is required as to when it is appropriate for MAHs to liaise with

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		local/regional/national data collection systems allowing patients and healthcare professionals (HCPs) to report suspected adverse reactions.
173 - 175		**Comment**: Signal detection is generally based on periodic monitoring within the MAHs safety database, with supplementary information being derived from the larger databases. The EMA mandates the monitoring of EudraVigilance, however the benefits over MAHs databases are yet to be established. **Proposed change** (if any): It should be clarified that "Signal detection is supplemented with the use of US FDA Adverse Event Reporting System (FAERS) or the database of the WHO Programme for International Drug Monitoring (VigiBase), with EudraVigilance being a legal requirement in EU."
188		**Comment**: Section IX.B.3 'Evaluation of the evidence supporting a signal' appears to describe signal validation (per definition on Lines 120-121). This should be made clear to avoid confusion. **Proposed change** (if any): **IX.B.3. Signal validation: Evaluation of the evidence supporting a signal**
220 - 222		**Comment**: In general, there is no established process for MAHs to review the quality of evidence supporting label changes in the EU for products marketed by other MAHs, for national/MRP/DCP approvals there is also no established process for obtaining English translated SmPCs for competitor SmPCs. It is also important to note that companies apply different scientific criteria for inclusion of ADRs into their SmPCs, inclusion of ADRs should be based on robust scientific practices established within the MAH.
223 - 224		**Comment**: For products which are no longer under patent and where multiple generics exist, it is difficult for MAHs to assess data beyond the scientific literature and their own. **Proposed change** (if any): It should be confirmed that this should be data held by the MAH only.

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235 - 245		**Comment**: This piece covers *decisions* that MAH could make i.e. closing signal, continuing to monitor, proposing actions. However no mention is made of *communicating* signals, so it is not clear what MAH should do next, or that this is covered in a later section. **Proposed change** (if any): ▪ proposing actions such as changes to the product information by means of a variation, if there is sufficient evidence of a causal relationship (see Section IX.C.3.)
238		**Comment**: It is suggested to include 'refuted signal' as a bullet point, so that this module is in line with the Periodic Benefit Risk Evaluation Report (PBRER) module. **Proposed change** (if any): Refute the signal as "false" signal based on medical judgement and scientific evaluation of the currently available information.
287 - 289		**Comment**: In the previous GVP Module, there was a requirement to track the signal management process from validation. **Proposed change** (if any): It should be confirmed where/when documentation begin during the signal management process
317-318		**Comment**: Please confirm which organisation is being referred to in section. There is also misalignment in the terms used validation refers to section IX.B.3 which concerns evaluation. **Proposed change** (if any): Add reference to Table IX.1.
326		**Comment**: MAHs perform the signal confirmation and signal analysis/prioritisation/assessment/recommendation steps globally. **Proposed change** (if any): A process to allow MAHs to contribute to the independent conclusions which have been drawn based on the data evaluated.
327		**Comment**: Expectations on MAH's monitoring of EudraVigilance data should be described more in details. Will

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		MAHs comply with the monitoring requirements by reviewing electronic reaction monitoring reports (eRMRs) and level 2B data for those DECs which turned out to be Signal of Disproportionate Reporting (SDRs)? Is it expected that MAHs review Level 1 data?
328 - 333		**Comment**: It is difficult to do without at times adding a qualitative aspect associated with data review within the database.
342 - 344		**Comment**: In general, there is no established process for MAHs to review the quality of evidence supporting label changes in the EU for products marketed by other MAHs. In addition for national/MRP/DCP approvals, there is also no established process for obtaining English translated SmPCs for competitor SmPCs to fulfil this requirement.
342 – 344		**Comment:** There is a constant high workload on marketing authorisation holders to assess all SmPC of the class to make sure the signal is/is not included in it. SmPC for other MAHs may get updated and this may be a continuous challenge. What is the expectation from EMA?
345 – 346		**Comment**: The word "recently" needs more clarification in terms of time interval.
347 - 348		**Comment**: Does this mean when a signal first originates from the EV data? What if MAH is already aware of signal (from global sources); also the MAH may already have the cases on EudraVigilance.
351 -354		**Comment**: This may be technically challenging based on the organisational structure of the MAH, single detection activities maybe spread across multiple users.
368		**Comment**: The term 'active substance' does not specify the brand for the MAH. Is the expectation that all products with the same active substances must be reviewed by all MAHs? **Proposed change** (if any): Can it be clarified that each MAH review their own products?
368 (Bayer)		**Comment:** Clarification of the word "review" is requested. Does this mean review of case narratives or disproportionality output?
368 - 371		**Comment**: It should be clarified whether the two weekly EudraVigilance review for products in the additional

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		monitoring list is recommended for EMA and NCAs or also for MAHs. If the intent is that EudraVigilance is monitored by both regulators and MAHs, it is suggested increasing the frequency to at least monthly periods. **Proposed change** (if any): A ~~two weeks' t~~ least an one month interval between reviews of EudraVigilance data is recommended for active substances contained in medicinal products included in the additional monitoring list in accordance with REG Art 23 (see GVP Module X), unless the sole reason for inclusion on the list is the request of a post-authorisation safety study (PASS).
386-387		**Comment:** Definition of validated signal in the legislation has been mapped to a stage where the signal that has undergone a full assessment by the MAH. As per lines 386 and 387, it further confirms that EMA would like to receive all documentation that supports the signal to be an emerging safety issue which can only be done after MAH's signal assessment. The timeline based on current definition has become very short as MAH still need to assess the signal rather than sending it at a triage stage of the signal (called validated previously).
401-405		**Comment**: Further clarification is sought on the definition of validation, MAHs complete a thorough evaluation before implementing label changes. **Proposed change** (if any): Further guidance on the definition of validation vs evaluation.
416 - 421		**Comment**: Amend the sentence to be in line with Figure XI.1. Notifications and procedural options for signals validated by marketing authorisation holders **Proposed change** (if any): For active substances included in the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), if by the time a marketing authorisation holder concludes that a signal is validated, and PSUR is due to be submitted in the following three months, the signal, together with any potentially related amendment to the product information, may be reported in the PSUR, unless the marketing authorisation holder considers that a variation application with supportive data should be submitted.
439		**Comment**: Depending on the complexity of the signal this timeline (as soon as possible and no later than 30 days after the signal is validated) may be too short for MAHs to come to a sound conclusion whether a variation

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		is required because this needs a thorough signal assessment and not just signal validation. The module should describe how to handle situations in which the MAH concludes that a variation is needed after the signal notification was sent out.
440 – 441		**Comment**: Examples are provided when a standalone signal notification is not to be sent. However, can it be confirmed whether case where a signal validation results in the decision of "monitoring the signal by reviewing new information from ICSRs or the scientific literature at appropriate time intervals to determine whether the new data are supportive of a causal relationship" is also covered?;
477 - 478		**Comment**: In addition to the information requested by PRAC opportunity needs to be given for MAHs to submit their conclusions on the signal assessment and recommended actions based on the conclusions for inclusion into recommendations from PRAC. **Proposed change** (if any): Marketing authorisation holders should collaborate with the PRAC for the assessment of the signals by providing the additional information requested [DIR Art 23(4) and REG Art 16(3a)] together with the MAH's conclusions and recommendations for actions (if any).
479 - 480		**Comment**: Based on the above an additional one month proposed for MAHs to provide conclusions and recommendations for actions. **Proposed change** (if any): The timeframe is agreed on a case-by-case basis. A typical timeframe is two months for submission of data and an additional month for submission of MAH conclusions and recommendations for actions. aA further two months is the timeframe for assessment by PRAC.
Figure IX.2		**Comment**: What is the level of information to be contained in this report, at a minimum to ensure that a MAH can adhere to global requirements it would be prudent to know, which of the four bullets in IX.C.4 Signal confirmation by Member States the signal is non-confirmed, and if possible the supporting data e.g. literature, MAHs safety database, clinical study data, non-clinical data, epidemiological study etc. **Proposed change** (if any): Further details of the information which will be communicated in the list of non-

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		confirmed signals should be provided.
Figure IX.4		**Comment**: It is proposed to include typical timeframes for actions for MAHs. **Proposed change** (if any): Additional data for all PRAC members (NAPs) and EMA (CAPs and NAPs) should be submitted within 2 months following request from data from PRAC. MAHs conclusions and recommendations for action should be submitted within 3 months following request for data from PRAC. Provide comments on preliminary assessment report within one month.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
Pharmacovigilance Astellas Pharma

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	This guidance is limited to the EU, EU-approved products, their MAHs and Eudravigilance. This guidance excludes almost any Signal Detection activities outside of the areas mentioned above. As such, integration with Signal Detection activities based on non-EU data, for example, may be (seriously) hampered. This would be counterproductive (and is not aligned to EU requirements).
	MAHs currently have processes to monitor the safety of their products according to GVP module IX (2012). Parts of these company processes seem to be duplicated by this new process, e.g. companies are performing signal detection and validation on EV data and EMA will also be planning to do this. From an efficiency point of view it would be useful to make only one party responsible. What is the expectation when there is a conflicting assessment of the signals (between MAH and PRAC assessor)?
	The word validation and confirmation should be specified in the context where used.
	We acknowledge that the steps in the process should be done on a case by case basis based on their nature (severity/impact), however, it would be useful to have even clearer guidance on expected timelines for all process steps (e.g. maximum duration, range).
	Answer to Question 1 The criteria for accessing case narratives is potentially too restrictive; if a signal is found outside of the EU will non-Astellas MAH EU data be fully accessible for evaluation? What level of detail does the MAH need to provide in order to get access to the case narratives and what are the timelines for providing the access?
	Answer to Question 2 More detailed guidance is required on risk-based approach e.g. for a mature product where the knowledge of the risk profile has been well established, and there are few reports received per year, 6-monthly monitoring may be too frequent to add value.
	Answer to Question 3 It is not clear what the reference time point is for determination of communication timelines is e.g. what is the detection date for an MAH? For ESIs in most companies an escalation process that takes some time between becoming aware of and confirmation of an ESI that makes definition of timeline important. What are the minimum requirements to report ESI and validated signals?

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')*
128-129, 138-139		**Comment:** In Signal Confirmation Step, it is stated that "signal confirmed does not imply that a causal relationship has been established". After this step, there is no description regarding in which step the causal relationship is established. **Proposed change (138-139, if any):** the process of evaluation of all available data relevant to a signal to determine the causal relationship and the need for any regulatory action.
263-264		**Comment:** Consider rephrasing "prioritization is a continuous process"? **Proposed change (if any):** Signal prioritization may be reassessed (increased/decreased priority) as new information becomes available.
326, 131-139		**Comment:** Table IX.1. As per this table it seems that the MAH has no role in the prioritization, analysis and assessment of (EU) signals and that this is the sole responsibility of the PRAC. MAH marketed compounds will have a comprehensive process to review global information from any source as part of their signal management process. Reading the definition for the terminology (lines 131-139) also may be perceived as suggesting that prioritization and evaluation is a task for the PRAC alone. **Proposed change (if any):** Clarify that this relates to EudraVigilance data only or change the roles and responsibilities in the table and clarify the text.
328-333		**Comment**: The text changes from "signals" to "Risks" without explanation of the relation between the two. **Proposed Change:** Such monitoring should be performed to determine whether there are new **signals** or whether risks have changed … etc.
338-340		**Comment**: Please clarify here in detail what access means and how it is granted or not (refer to answer to Question 1)
341		"The review of the electronic reaction monitoring report suggests a signal " **Comment**: Proper signal detection involves all kinds of sources: a signal arising from other sources (e.g. FAERS) can be strengthened by access to EV data.

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		Proposed change: a signal is identified after review of the electronic reaction monitoring report or other sources, for which proper rationale should be provided.
371		**Comment:"** A monthly monitoring of EudraVigilance data is routinely applied by the Agency for other active substances." This text is a little vague. Since this chapter concerns "Marketing authorisation holders, the national competent authorities and the Agency", it would helpful to give guidance to MAHs here. We question the appropriateness of monthly monitoring. In many cases, less frequent may be adequate. **Proposed change (if any):** Monthly monitoring of EudraVigilance data is routinely applied by the Agency for other active substances. MAHs are advised to follow this frequency, unless well documented grounds give reason to deviate.
401		**Comment**: When a signal is validated by MAH, is it correct to say that sometimes a variation is to be submitted, without PRAC's review? If a signal leads to a variation, it is submitted to the relevant competent authorities and not to the PRAC. How does the PRAC maintain oversight of the new, ongoing and closed signals? Also, timelines for validation and evaluation by MAH are unclear. There is guidance to communicate the results of the validation to the assessor. It would be helpful to have additional guidance on timelines for the detection – validation process.
401-405		**Comment:** The timelines for submission of variation (3 months after signal is validated) are short and do not fully take into account the time for MAH to evaluate/assess the signal in order to take appropriate actions. Is the intention that signal validation includes the full comprehensive evaluation performed by the MAH as well? **Proposed change (if any):** Variation application should be submitted after full evaluation of the signal taking into account all appropriate data sources.
435-438		**Comment:"** When a validated signal does not meet any of the conditions outlined in IX.C.3.1., IX.C.3.2. or 435 IX.C.3.3., the marketing authorisation holder should complete the signal validation form available on the European medicines web-portal and send it via [functional e-mail address tbc] to the Agency and national competent authorities." Therefore, the MAH can only send validated signals to the Agency. This ignores the fact (and the requirement) that MAH already have a fully functional Signal Detection process that includes detection-validation-

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		confirmation/evaluation and action. **Proposed change (if any):** The MAH should at least send validated EV signals, however, fully evaluated signals, both based on EV as well as other data sources will be accepted by the Agency for inclusion in their process.
452-459		**Comment**: It seems that PRAC will be by-passed "when the data does not warrant further analysis" : criteria to determine this appear vague. Paragraph is confusing; please provide examples. How does the PRAC maintain oversight of the new, ongoing and closed signals?
470-482		**Comment**:" The PRAC prioritises signals..", "the PRAC appoints a rapporteur..", "rapporteur should transmit to the PRAC an assessment report which should include a proposed recommendation. Marketing authorisation holders should collaborate with the PRAC for the assessment of the signals by providing the additional information requested" Does the PRAC have the sole prerogative to assess signals? **Proposed change (if any):** [Add] Signals confirmed and assessed/evaluated by MAHs will be re-assessed/reviewed by PRAC.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
477-479		"Marketing authorisation holders should collaborate with the PRAC for the assessment of the signals by providing the additional information requested" **Comment:** Please provide clarification on the nature and details of information requests during the validation, confirmation and information requests. NOTE: The Eudravigilance database contains EU ADR data and ex-EU SUSAR like data, hence detailed case information will be accessible for the Rapporteurs and PRAC. **Proposed Change:** Marketing authorisation holders should collaborate with the PRAC for the assessment of the signals by providing the additional information *(such as: xxx ?tbc)* requested.
480-481		"Time tables of signal assessment published on ….agency's website" **Comment:** Will methodologies used for assessment of the signals be published or shared with MAH?
483-484, 416-422		" When PRAC recommends assessment ….within another procedure e.g. PSUR" **Comment:** Please clarify when the PRAC will recommend that assessment is done via PSUR and MAH is to be responsible for signal assessment. If a PSUR is to be submitted within 3 months and the signal evaluation process has already started the DLP may have already passed. Is the MAH expected to prepare a full comprehensive analysis of the signal within that PSUR e.g. as late breaking information? If so, this may be challenging under the current timelines.
487-488, 554		"PRAC recommendation….. follow up discussion on the signal" **Comment:** What does follow up discussion imply? Will MAH be involved in follow up discussion? Does this refer to the step where MAH provides comments on preliminary assessment report in the flowchart? What are the timelines for this process? There is no explanation for this process in the text.
547 (Figure IX.2)		**Comment:** When MAH detected a signal and validated the signal, MAH continues to do further evaluation/assessment of the signal in order to take appropriate actions. When the signal is in the list of non-confirmed signal that MAH receives, should MAH not continue the assessment of the signal?
547-555		**Comment:** Flowcharts are useful however inclusion of timing/timelines is selective and unclear. (see also comment on line 401) **Proposed change (if any):** Please add timelines to flow charts

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553, 554		**Comment:** The language regarding PRAC recommendation in the flowchart is unclear. The apparent duplication seems to concern "Recommendation on prioritisation" in the upper part, while the recommendation in the lower part concerns approval of any changes suggested by PRAC rapporteur **Proposed change (if any):** Specify: "Recommendation on prioritisation" and "recommendation on evaluation"

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
Baxter Healthcare Corp.

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Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Consider adding in a definition for a refuted signal, especially since this is referred to in GVP VII. Definition of a refuted signal: A signal that has undergone signal analysis and signal assessment and it is determined that no further action is required and the signal was closed.
	Response to General question 1: Are the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders acceptable (see IX.C.2.1.)? Yes, provided MAHs have the ability to request narratives as needed
	Response to General question 2: Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable (see IX.C.2.2.)? Yes
	Response to General question 3: Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable (see IX.C.3.)? Identifying an emerging safety concern based on new PV data can originate from analysis of aggregate data from one or different sources during routine signal management activities or ad hoc, e.g. a new publication of safety data from a clinical study. Signals potentially impacting risk-benefit balance of a medicinal product and/or public health should be communicated ASAP to the authorities. However, the guidance on 2 working days from becoming aware of the issue is not fully clear and sufficient for preparing a notification to competent authorities. Expectation of what is considered the awareness date is not clear enough in this guidance. Normally, awareness date would be at the time a MAH has analysed and evaluated available safety data with a documented medical conclusion that it might impact benefit-risk of a product. Moreover, emerging safety concern is suggested to be notified at latest within 5 (five) calendar days from becoming aware, in order to ensure the MAH at notification appropriately can describe the safety concern and provide the

Stakeholder number *(To be completed by the Agency)*	General comment
	source(s) of information, relevant documentation and information on any planned or taken actions.

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')*
122		Comment: Add clarification for the heading "Signal confirmation". Other headings define "by the", ensuring consistency with defining the roles and responsibilities Proposed change (if any): Signal confirmation by the Competent Authority or the PRAC Rapporteur
347-348		Comment: Add clarification. To ensure that if the review of a subset of narratives results in enough justification for an action that not all case narratives need to be reviewed, therefore removing the word "corresponding". Proposed change (if any): When a signal originates from EudraVigilance data, marketing authorisation holders should review the ~~corresponding~~ case narratives as part of the signal validation."
385-386		Comment: Please refer to response to General question 3. Consider increasing the timeframe to allow the MAH to gather enough relevant data. Proposed change (if any): This should be done as soon as possible and no later than 5 calendar days.
404-405		Comment: Consider increasing the timeframe to allow the MAHs to manage regulatory submissions. Add guidance on signals already considered by PRAC. Proposed change (if any): This should be done as soon as possible and no later than 6 months after the signal is validated. In case signal is already considered by PRAC, PRAC recommendation should be followed, or awaited, as appropriate. The timing of the submission will also be dependent on local regulations/restrictions.
439		Comment: Signal should only be forwarded if the signal has not been refuted. Also the signal should be forwarded after assessment rather than validation, since signal validation still requires further analysis. Proposed change (if any):" This should be done as soon as possible and no later than 30 days after the signal is assessed and analysed. If the signal has been refuted within this timeframe, the signal does not require

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Bristol-Myers Squibb

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	1. Regarding the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders, the proposed criteria provide insufficient information to fully assess the signal accurately. If the expectation is to monitor EudraVigilance then the availability of additional details would be required to accurately evaluate the data. Although it is understandable to provide restrictions to protect personal data, acceptable feedback is dependent on the content and detail of the electronic reaction monitoring report and ease of searching the web-portal (not yet built) which are critical unknown factors (which make providing feedback difficult).
	2. Two week monitoring of EV database would be too frequent for the collection of any meaningful data. It may be preferred to conduct monitoring on a 6-month basis, which would allow for time and data to accrue
	3. Regarding the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders, more clarification of the communication for validated signals dependent on source (member state vs MAH) would be appreciated
	4. Please provide clarification of roles and responsibilities with timelines. Following the 30 days of PRAC review, when will MAH be expected to respond 5. TableIX.1 and figure IX.2 indicate the role of the MAH in the EU signal detection process is to identify and submit validated signals within 30 days. It appears that all validated signals will then be confirmed and analyzed by PRAC, and not by the MAH. Is it the intention of PRAC to remove the MAH from the process of assessment, confirmation and actions for all validated signals? 6. If so, can PRAC provide justification for this approach? BMS believes that the MAH should have in place a robust signal detection process that includes analysis and confirmation or refutation. The MAH should continue its assessment of validated signals as part of its obligation to understand and communicate the safety profile of the product, and take appropriate measures in EU and in other global markets. In the EU, there is currently a mechanism for notification to the EMA of validated signals via the PSUR process. Additionally, the requirements around rapid communication of emerging safety information will assure that critical safety concerns are promptly identified and communicated to EMA. Given the MAH's obligation to maintain a scientifically up to date label for authorized products, it is appropriate to expect that the MAH will promptly notify EMA

Stakeholder number *(To be completed by the Agency)*	General comment
	when a signal assessment results in the need to update product labeling, or other safety related activity.

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14.10.2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

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

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Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	
	1.	

Answers to specific questions:

1. **Are the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders acceptable (see IX.C.2.1.)? These criteria have been developed to prevent unjustified download of case narratives, in relation to Annex C (Confidentiality Undertaking for Marketing Authorisation Holders) of the EudraVigilance Access Policy which aims at ensuring the protection of personal data.**

   In general the proposed criteria for access to case narratives held in EudraVigilance are acceptable for the MAH.

   However, it should be considered that some companies have only few reportable serious ICSR so that a signal need not/cannot necessarily be detected by an electronic reaction monitoring. Therefore an additional/alternative criterion instead of an electronic monitoring report is required. As possible second criterion/alternative it is suggested that the QPPV confirms (date of confirmation = day 0) that the signal is validated by the MAH.

2. **Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable (see IX.C.2.2.)?**

   Without having knowledge of EVDAS training materials and proofing access policy in practice it seems that for monitoring of EudraVigilance data and considering only signals related to an adverse reaction the recommendations regarding the frequency of every two weeks for active substances contained in medicinal products under additional monitoring and a monitoring period between 1 - 6 month depending on the identified risk, the potential risk and the need for additional information on medicinal products or active substance is acceptable as long as following circumstances are available:

   - identification of single ICSRs via various filter functions,
   - user-friendly download tools (current available exports manager for MLM ICSRs is not suitable,

   Otherwise the mentioned frequencies for reviewing EudraVigilance data are NOT feasible in practice!

   Clarification is needed for which substances a monthly monitoring and for which substances a 6 months review is expected. Can the MAH decide about and determine the interval - which in no case is longer than 6 months - depending on the benefit-risk- profile of the active ingredient?

3. **Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable (see IX.C.3.)?**

In general the proposed modalities for communication of emerging safety issues and validated signals by marketing authorisation holders are clear and acceptable.

The timeline of two working days for notifying an emerging safety issue in writing to the relevant competent authority and to EMA mailbox is considered as too short. An adequate timeline of at least 15 calendar days (similar to ICSR reporting obligation) is proposed.

IX C. 3. 3: The text of chapter C. 3. 3. is not in full accordance with figure IX which explains the process very well and much better than the text. The text does not refer to the situation in which a PSUR has to be sent within the next 3 months.

IX C. 3. 1: With the new module IX the change of product information cannot be an ESI anymore. Relevant changes of the product information are Type Ib variations to which the reaction of the competent authorities is required before the change can be realized. To avoid significant periods of out of stock situation and to enable a safety relevant change of product information as quickly as possible it should be possible to initiate such change as an ESI as well.

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
BPI Service GmbH

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Use of modal verb shall: it is noticeable that the verb shall is only rarely used. Could you please confirm that this is the intention? In that case the module provides guidance but MAHs can do differently as long as it is reasonable, documented and traceable, e.g. with regards to monitoring frequency of Eudravigilance data.
	1. Are the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders acceptable (see IX.C.2.1.)? Comment: the criteria seem acceptable as long as the process allows timely access to case narratives. Would it be an option to generally allow access to case narratives for any report from literature, regardless of the MLM status of the substance?
	2. Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable (see IX.C.2.2.)? The recommendations regarding the frequency seem acceptable. However for products with a very low number of reports monitoring of Eudravigilance data every 6 months might cause additional workload for MAH without any recognisable benefit. The guidance in the module should consider such circumstances and allow longer periods of monitoring of Eudravigilance data, when MAHs can justify this decision.
	3. Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable (see IX.C.3.)? The period of 2 days for notifying the authorities of Emerging Safety Issues seems too short. A 7 or 15 day timeline would be more practical.

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')*
338-348		Comment: In the process of signal detection is might quite often be necessary to review case narratives to decide whether or not a case report (or case reports) constitutes a signal. Could you please provide details on how to apply for access to case narratives? How long will it take until access is granted? Will access be granted on a case to case basis or per substance for a period of time? Proposed change (if any):
290-292		Comment: Could you provide additional guidance on the timelines for request of documentation? Proposed change (if any):
434-446		Comment: Reporting of signals as standalone signal notification: is the intention to report all signals regardless of the importance? Could you please clarify? Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 September 2016

Submission of comments on GVP Module VI – Management and reporting of adverse reactions to medicinal products (EMA/873138/2011 Rev. 2)

Comments from:

Name of organisation or individual
CSL Behring

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	
	Questions on which the Agency seeks specific feedback: **1. Are the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders acceptable (see IX.C.2.1.)?** In principle, most of the proposed criteria are acceptable. However, there are certain situations where the assessment of case narratives would be beneficial that are not accounted for by the proposed criteria. One such situation is the potential increase in frequency/severity of a known safety concern. Pinpointing increase in severity may require assessment of case narratives, but this is not allowed for under the second criteria, where the 'signal is not addressed in the product information' for any product with the same active substance. **2. Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable (see IX.C.2.2.)?** In terms of monitoring frequency, the suggestion for monthly monitoring would be very onerous and provide very little benefit for certain products (eg. Those with small numbers of ICSRs per year, or those with a long history of post-authorisation exposure-such as 20+ years). However, the draft module does allow some flexibility with regard to this, and recommends a maximum interval of six months. On the basis of this flexibility, the recommendations appear acceptable.	

Stakeholder number *(To be completed by the Agency)*	General comment	
	3. Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable (see IX.C.3.)? The timelines for communication are indicated clearly in the module. However, some consideration needs to be given as to the practicalities for submission of a variation within three months of signal validation. This timeline is significantly shorter than expectations that have been communicated previously via member state inspectorates, such as MHRA, where a maximum timeline of six months was recently communicated (see slide 10): http://www.pvinspections.glasgows.org/files/pv/3%20R.%20Webb%20-%20Reference%20Safety%20Information%20and%20Pharmacovigilance.pdf Whilst the importance of prompt submission of variations regarding important risks is acknowledged, the application of this timeline across all submissions including non-serious events (for example headache, myalgia, diarrhoea) may impact the ability of MAH to appropriately prioritise variation submissions for important risks. A pragmatic timeline that would allow MAH the ability to prioritise variation submissions to allow for more timely submission of serious events over non-serious events would be six months. Concerning the submission via the stand-alone signal notification route, insufficient information has been provided at the time of this consultation period to comment on this. Requesting further public comment on this aspect once the 'signal validation form' has been made available would be appreciated.	

Stakeholder number *(To be completed by the Agency)*	General comment	
	Other comments: - One of the key pieces to this proposed revision of Module IX is the 'signal validation form' (line 436). The assessment and comment that we are able to provide in the absence of a draft of this form is incomplete, as it is not clear exactly what the expectation is in relation to the level of information that MAH will need to provide, and therefore whether the timelines and other details in relation to this are appropriate. - MAH have obligations to worldwide regulatory authorities outside EMA. As such, MAH follow guidance in addition to GVP concerning signal detection, including CIOMS VIII. CIOMS VIII describes the process of signal prioritisation undertaken by MAH (chapter IX, section a). The expectation in this draft module that signal prioritisation is a process undertaken by PRAC and not MAH is impractical in this context. Consideration should be given to aligning the contents of GVP Module IX with the expectations for MAH in CIOMS VIII. The module would benefit from the use of terminology with CIOMS VIII, the insertion of a signal prioritisation step for MAH prior to signal validation (Signal validation is referred to as Signal Evaluation in CIOMS VIII), and perhaps referring to the signal prioritisation step by PRAC under a different name, such as 'PRAC Workload Prioritisation'. The obligations for MAH also extend to consideration of actions such as DHCP letters, risks management plan update etc. These must be done independently of any such assessment and recommendation by PRAC if the MAH deems it	

Stakeholder number *(To be completed by the Agency)*	General comment	
	necessary for all markets. The module does not appear to consider the implications of this, and if such activities are considered by PRAC in its own recommendations. - The clarification of the steps of signal management and the roles and responsibilities in relation to this provided in this module will likely result in significant process and system modifications in relation to this for some MAH. It is requested that sufficient lead time be provided between the publication of the final version of the module and the anticipated date coming into effect to allow for this. Given that comments are being sought on the draft revision, it is anticipated that some changes may be made on the basis of these comments prior to publication of the final version. As the extent of these changes is not clear, it is not practical for MAH to fully implement process changes in advance of the final module becoming available.	

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')*	
118-121		Comment: The definition of signal validation appears quite soft here, but other parts of the module, it implies a full signal evaluation as described in CIOMS VIII (Section IX.B.3). Proposed change (if any): Align with 'The process of evaluating the data supporting a detected signal in order to determine whether there is sufficient evidence to indicate a causal link between the event and the administration of the product'.	
122		Comment: The term 'signal confirmation' is misleading, as it implies that this step confirms if the evidence supports that the signal reflects a true change to the safety profile- ie. the signal is confirmed following evaluation. This is not at all what is occurring during this step, which is described as a triage function for PRAC. Some validated signals may not go to PRAC purely because they are being handled through a variation procedure (see IX.C.4, line 452), not because there is insufficient evidence. Proposed change (if any): Re-name as 'Assessment of PRAC review requirement'	
131		Comment: Per comment provided above in the general section, the terminology of signal prioritisation is in conflict	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		with the meaning in CIOMS VIII, where it is a step undertaken by MAH. Proposed change (if any): Re-name as 'PRAC signal analysis and triage'
188		Comment: It is not clear from the heading name if this is referring to signal validation or if it is general advice relating to signal assessment. Line 121 appears to indicate that this is signal validation. Proposed change (if any): Re-name heading 'Evaluation of evidence during signal validation' for clarity
331-333		Comment: Whilst the overall aim of the signal detection and management process is to detect new risks or changes to known risks, this is not the aim of the specific activity of Eudravigilance monitoring. Proposed change (if any): 'Such monitoring should be performed to determine whether there are any signals of disproportionate reporting that should be considered for further investigation. The outputs of Eudravigilance monitoring should be considered in the context of other available data, and clinical judgement should be applied. Further detail may be found in GVP Module IX Add 1.'

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	
378-379		Comment: It is not clear whether the wording 'signals they have validated' refers to anything which has been through the validation process or only items which have been determined to have a reasonable suspicion of a causal link to the product. Proposed change (if any): - Change to 'MAH have to inform competent authorities of validated signals'. - Provide a definition of a 'validated signal' in IX.A.1- ie. signals which have been fully evaluated and have been determined to have at least a possible causal link to the administration of the product (or similar).	
439		Comment: The timeline of 30 days is shorter than notification via other mechanisms for validated signals with stronger evidence/implications. Proposed change (if any): Align timeline with the notification via PSURs of 3 months.	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

October 14, 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
[redacted] Dr. Ebeling & Assoc. GmbH, [redacted]

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	See 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')*
Line 118f. vs Line 244f. vs Line 402		Comment: There is a discrepancy between just to 'verify that further analysis is justified' and 'proposing actions such as changes to the product information'. The latter needs a complete assessment process at the single MAH level which corresponds to the conclusive decisions of PRAC at EU level addressed as 'Signal analysis and prioritisation, assessment, recommend-dation'. It is important to clarify that the process of signal assessment including conclusions (further actions or no action required) is an essential part of the signal management of the MAH as it has to be if the MAH is supposed to 'propose changes to the product information and/or the RMP' and that the role of PRAC/CAs is to make decisions for the EU (also including extended aspects as e.g. class effects). Proposed change (if any):
Line 406 and Line 421		Comment: How is it guaranteed that information from variations will be automatically further assessed for further actions on EU level? Is there any guidance addressing this process? Wrt PSURs a procedure is defined. Proposed change (if any):
Line 442f.		Comment: The circumstance that a safety-relevant issue mentioned in one SmPC/PIL within the EU does automatically exclude the characterisation as signal may be misunderstood as for the single MAH any safety-relevant information outlined in other SmPCs/PILs on the same API with a similar risk profile of the product from other MAHs may, of course, represent a signal(s) for a specific MAH. Btw, to "outsource" the characterisation as "non-signal" of a risk in case that at least one SmPC/PIL in the EU does address it might be justified from the EU-perspective of a regulatory body but a specific MAH will handle this information like any other signal from 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')*
		other source. However, to exclude the 'Standalone signal notification' in these situations may be justified if there is a robust system for consequent procedures resulting from safety-related variation(s) (see also previous comment). Proposed change (if any):
Line 543/547		Comment: The figures are describing the 'notification by MAH' and the 'confirmation by PRAC'. This is misleading as also the MAH is confirming signals when the MAH submits variations to update the safety-related information. The PRAC is responsible for 'Harmonisation' of the signals within the EU if one is looking at the whole "Signal Scenario" in the EU. However, for pure CA-originated signals (e.g. from statistical signal detection in EV) the PRAC also confirms. The current draft guidance with GVP Module IX (Rev. 1) may further enhance the misleading interpretation that the MAH should only communicate simple information on any news where verificatory action is considered as justified and that the PRAC is doing the further assessment. The described activities of the MAH in terms of 'validation' together with the term 'notification' will give the impression that the role of the MAH is very restricted. This is in contrast to the expectation outlined in the same guidance (Line 188 ff.) that the MAH should do a validation of the signal and if applicable propose specific recommendations for actions. This means in essence that 'validation' is a synonym of 'evaluation' as described in IX.B.3. Otherwise it would not be possible for the MAH to draw any conclusions and only waiting of a CA decision would be possible.
General		Comment: (The more general comments are given here and not in 1. as one should first read the specific ones.)

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		A: There is a terminology issue involved in the description of the signal management process. The terminus signal in the GVP module IX (not only there) is also used for situations where it is a question of risk (whether potential or identified). The definition of signal ends with the concluded verificatory action. Once this action is done the signal might further on be refuted or transformed to a new risk. If the current concept of signal as used in this GVP module IX should be maintained one has to define potential or identified risks as "listed", i.e. already mentioned in the SmPC/PIL, or to introduce the risk term into the signal management process at the stage where the verificatory action was done and the evidence does not allow to refute the signal. B: As addressed in several discussions with lawyers specialised in drug law the concept of responsibility/liability of the single MAH for a medicinal product does not end with any decision by regulatory authority (CA) or institution (PRAC). If e.g. the CA/PRAC does have a contrary position to the MAH and wants to skip a new risk in the variation of the SmPC/PIL or within the RMP as applied for or described by the MAH the exclusion of the risk in case of false negative constellation does not impede or preclude a judge to hold the MAH guilty and to apply for liability issues if there was any harm. This should be considered in the policy for improvement of drug safety which has been comprehensively initiated with the EU wide introduction of the signal management guidance.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016

Submission of EFPIA comments on *Guideline on good pharmacovigilance practices (GVP)* – ***Module IX and Addendum I***

Comments from:

Name of organisation or individual
EFPIA [redacted]

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1. General comments

Stakeholder number	General comments
	EFPIA welcomes the opportunity to provide comments on Draft guideline on good pharmacovigilance practices (GVP) - Module IX – Signal management (Rev. 1) and Addendum I. We have consolidated our comments within this same document.
	Role of the MAH Signal management is a pivotal process for the MAH as a key responsibility for patient safety. The revisions to the module appear to diminish the responsibilities of the MAH. This must be appropriately defined to reflect the role of the MAH as outlined in GVP Module 1. This revised module covers signal management by the Agency and NCAs, but the role of MAHs is substantially diminished, particularly where the MAH is the originator of the medicinal product. The scope of obligatory actions by the MAH according to this revision is limited to signal detection and validation, whereas most MAHs have standard practices and are accountable for: • Signal detection (determining when a safety observation becomes a signal) • Prioritization & evaluation of signals • Confirmation of new risks Planning and implementing actions The responsibilities of MAHs should be fully recognised and specified within GVP IX (Rev 1), and it should be acknowledged that MAH processes are different from those of the Competent Authorities. Signal detection in EudraVigilance (EV) is just one of a series of analyses involving multiple MAHs, multiple regions and other regulatory authorities all of whom conduct independent evaluations. These assessments involve research of databases and sources of information other than EV, and include MAH databases. Different outcomes are inevitable. Examples of the expectations of Agency in non-harmonised outcomes would be helpful. In addition, as the timing of each step conducted by the various stakeholders across the globe will vary there will be further conflicts of outcomes across time. As the conclusions of signal evaluations conducted by the various stakeholders may also differ, MAHs may have to initiate a series of actions based on varying conclusions. This could lead to different actions taken in the EU and other regions of the world. Harmonisation would be aided by the addition of a macro process flow diagram outlining the main steps. EFPIA would welcome the provision of indicative timings within this diagram. Any differences in the responsibilities of the originator MAH when compared to manufacturers of generics, should be specified in the text, not least where the bulk of the safety data are held by generic manufacturers.
	Signal validation Signal validation is defined [EU) No 520/2012 Article 21] as: "the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis." MAHs have adopted this definition and are broadly aligned with it. However, the term 'signal validation' is used inconsistently throughout this revised document. Signal validation should refer to the day on which a decision is made that a signal requiring further evaluation exists. This translates to Day 0 for the

Stakeholder number	General comments
	remainder of the process. Individual examples of inconsistencies are highlighted within the specific comments in Section 2. Until the existing inconsistencies are clarified, MAHs will be not able to comply with Module IX as revised here. On this basis it is vital that the existing definition is confirmed and used consistently throughout the module.
	Effective date The proposed effective date for the revised guideline (1Q2017) should be aligned with the date when MAHs will be able to monitor and access data in EudraVigilance for signal detection. This will allow MAHs to adapt, enhance or create aligned systems and processes. It is our view that an effective date in November 2017 is pragmatic.
	Processes **Monitoring of EudraVigilance data** MAHs recognize that EudraVigilance is an important source of potential signals, but many other sources are equally relevant. Monitoring and aggregate analyses of signals must integrate all relevant sources, rather than focusing on one database which may have less statistical power than a pooled and/or integrated safety data population made possible by existing or emerging technologies. In the absence of full insight into the contents of eRMRs for products with developing safety profiles and other outputs from EVDAS it is difficult to assess what obligations MAHs face at this time. Our view is that the effort involved in operationalising the integration of the outputs from EV into MAH systems could be disproportionate to the value provided in a public health context. **New requirement for population-specific signal management** EFPIA takes note of the requirement to implement routine signal detection in specific patient populations {paediatric and non-paediatric groups and geriatric and non-geriatric groups (Module IX Addendum I)}. It will take time for MAHs to develop and implement signal management for sub-populations as a standard procedure. **Definitions** A definition of Day 0 of a signal is missing; this should be the date of signal validation. Several references are made to the provision of RMP and PSUR as a source of signals. These documents should be a summary of signals; they are not for the purpose of signal detection. The wording relating to which signals need to be the subject of communications is ambiguous. The guideline should specify that this requirement applies only to evaluated signals that have indicated a new risk.

2. EFPIA responses to the questions raised by the EMA

Stakeholder number	*EFPIA responses*
	Response to Question 1 Generally the criteria for access to EudraVigilance are acceptable, with the following requests from EFPIA companies: • MAHs have a requirement to access narratives regardless of the origin of the signal (current limitation is for signals originating from eRMRs). Review of all narratives regardless of whether a signal inclusion in the product information or labelling (for example a signal under review may already be related to a labelled event or there may be a change in nature of an already identified risk under review resulting in a new signal) would be helpful at the time of medical evaluation to support evidence-based decision making on whether a signal has been detected. • The proposed process which requires the submission of a request for case narratives is cumbersome and will slow down signal validation. We request access is granted to qualified personnel to review selected ICSRs including narratives. •
	Response to Question 2 The recommendations for monitoring of EudraVigilance are generally sufficiently detailed, whilst providing a degree of flexibility to adjust the frequency based on the characteristics of the medicinal product, the safety topic, the time since first authorisation, and most relevant data sources. The proposed frequency for established products with a well-documented safety profile could justifiably be reduced to once yearly as per the risk based approach in IX.C.2.2. It is difficult to assess the true impact on workload without a greater understanding of the EVDAS system, and how it is structured or will be performed.The following question was raised: • Could the Agency make public the frequency of monitoring EudraVigilance for specific substances? If this is done MAHs can align with the periodicity of the signal detection activities. •
	Responses to Question 3 Emerging safety issues: The timelines are clear & acceptable as long the Agency defines and clarifies what constitutes "becoming aware of the issue." From an MAH point of view the clock starts from the point at which a decision is made that a new safety issue is a validated signal. However, some timelines are unclear. In line 385 it is noted an ESI should be reported in 2 days, however in lines 417 to 419 state: " if by the time a MAH concludes that a signal is validated, a PSUR is due to be submitted in the following 3 months, the signal, together with any potentially related amendment to the product information may be reported in the PSUR. The suggested timelines for a validated signal, if a PSUR is not due to be prepared, means that a validated signal, which is not yet considered a risk, and may not fulfil the criteria for an important risk, needs to be communicated to EMA within 30 days. This could be a risk of nausea and on a product where the next PSUR is due several years in the future. An update in 30 days only makes sense for a medically important risk.

Stakeholder number	*EFPIA responses*
	Proposed changes: Urgent signals/medically important signals must be notified within 3 business days. Medically important signals should be notified within 30 calendar days. Non-important signals should be notified either within 3 months' from the point of recognition, or in the next scheduled PSUR. Valid signal: requires a complete revision, based upon the general comment concerning signal validation.

3. Specific comments on GVP Module IX

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
100		**Comment:** Changes in population distribution should be included as a possible cause for raising a signal and as the text refers to known association, this should be adverse reaction, rather than adverse event **Proposed change:** New aspects of a known association may include changes in **distribution (e.g. gender, age and country),** frequency, duration, severity or outcome of the adverse ~~event~~ **reaction**.
112		**Comment:** The EU signal management process described is that of the EMA and Competent authorities, it should be noted that MAHs processes may differ. **Proposed change:** The EU signal management process includes the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment and recommendation for action [IR Art 21(1)]. **MAHs may have an alternative process but should encompass the general principles of the EU signal management process.**
128		**Comment**: Confirmation of a new aspect of a known association should be included. **Proposed change:** Add: "nor a new aspect of a known association" i.e. "The fact that a signal is confirmed does not imply that a causal relationship **nor a new aspect of a known association** has been established, but that the signal should be discussed at EU level and further investigated by PRAC (see IX.C.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')*
147-152		**Comment:** In this definition, Emerging safety issue applies to authorised medicinal products and GVP Module VI is referenced. However, in GVP Module VI (Rev 2) Section VI.C.2.2.7., the notification of emerging safety issues is also applicable in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation, when information (quality, non-clinical, clinical) that could impact on the risk-benefit balance of the medicinal product under evaluation may become available to the applicant. **Proposed change**: A safety issue considered by a marketing authorisation holder in relation to an authorised medicinal product **(or product in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation**) under its responsibility to require urgent attention of the competent authority because of the potential major impact on the risk-benefit balance of the product and/or on patient or public health, that could warrant prompt regulatory action and communication to patients and healthcare professionals.
161-172		**Comment:** Although implied with current text consider to make clear that sources for identifying signals can also stem from information within a drug class and in addition may not be limited to drugs used for one indication. **Proposed change**: Add: "information on class effects" and "information from use in other indication(s)".
163		**Comment:** This text is tailored to the process at the NCA/Agency level. However, as the MAH also performs signal detection, the sources for signals should apply to the MAH as well. **Proposed change:** "... provided ~~by marketing authorisation holders~~ in the context of regulatory procedures (e.g. Risk..."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
173-175		**Comment:** Signal detection is generally based on periodic monitoring within the MAHs safety database, with supplementary information being derived from the larger databases. **Proposed change**: To clarify that signal detection is supplemented with the use of US FDA Adverse Event Reporting System (FAERS) or the database of the WHO Programme for International Drug Monitoring (VigiBase), with EudraVigilance a legal requirement in EU.
178		**Comment:** It is explained that signal detection methodology depends on the nature of data and type of medicinal product. However, the applied signal detection activities and their frequency of execution also depend on the characteristics of medicinal products, e.g. time on market, local versus global exposure, population, and others. **Proposed change**: "…on type **and characteristics** of medicinal product concerned…"
195		**Comment:** Epidemiology should be added as supportive information in relation to signal validation. **Proposed change:** … supportive results of relevant investigations, **information on epidemiology;**
215-216		**Comment:** Changes in "duration" of an ADR are considered to be a signal (see signal definition in section A.1) **Proposed change:** … additional insight on an expected reaction in terms of e.g. its severity, **duration**, …
235-243		**Comment:** Clarification should be provided if the signals where an evaluation results in a decision to continue monitoring are to be classified as "unvalidated signals" (as described in the 2012 version Signal validation section "it may be appropriate to continue to monitor the potential signal until there is enough evidence to confirm the signal"), or "validated signals to be monitored". Significant changes to the text are proposed below. **Proposed change**: "The evaluation of the evidence may involve several rounds of expert discussions and different levels of decision-making, within individual organisations. This may result in one of three decisions, as follows: - Refuting the signal, when the available data are not sufficient to support a new causal relationship, a change in characterisation of an existing causal relationship, or a new or change to an existing potential risk (a new signal may be re-opened at a later stage if new evidence arises); - Confirming a new, or change to an existing, potential risk, requiring further risk assessment by reviewing new information from the ICSRs or the scientific literature at appropriate time intervals to determine whether new data are supportive of a causal relationship;

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		- Confirming a new, or change to an existing, identified risk, proposing actions such as changes to the product information by means of a variation, or other routine or additional risk minimisation measures, if there is sufficient evidence of a causal relationship.
263		**Comment**: How a signal is managed depends on the prioritisation and this defines the timelines, add reference to these. **Proposed change:** Add "For timelines refer to IX.C.3"
IX.B.5 Lines 269-294		**Comment**: This section only refers to MAHs being required to provide documented evidence of appropriate signal management practices but can the Agency confirm that these quality system requirements will apply across all MS who are delegated signal detection responsibilities in EV for NAPs and medicinal products authorised via MRP/ DCP? How will the HMA or the Agency ensure that all MS staff are performing signal management activities consistently and are trained appropriately? Signal detection responsibilities should follow the same expectations as the MAHs. **Proposed change**: Through the HMA, MS will ensure that any signal detection delegated to a MS for e.g. nationally authorised or MRP/ DCP authorised products is subject to quality management principles.
299		**Comment:** In order to avoid any uncertainties, please mention that both MAHs and CAs should monitor the safety of medicinal products in the EudraVigilance database. **Proposed change**: Just below the heading, please add: "Marketing Authorisation Holders and Competent Authorities should monitor the safety of medicinal products in the EudraVigilance database."
331-333		**Comment:** It is stated that monitoring of EV should be performed to determine new or changed risks. It is not mentioned that it should be performed to detect signals. Recommend adding clearer intention for EV monitoring by stakeholders. **Proposed change:** Add "Monitoring of EudraVigilance is a mandated signal detection activity according to the DIR."
Lines 338-340		**Comment:** There is no timeline provided for the Agency to grant narrative access for the MAH. **Proposed change:** Please consider addition of a timeline for narrative access for 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')*
341		**Comment:** "The review of the electronic reaction monitoring report suggests a signal (see IX.A.); " First time the electronic reaction monitoring report is mentioned in the document – this report should be more clearly defined. **Proposed change**: Define earlier in document.
347-348		**Comment:** The wording confuses the concept of a signal before and after validation. Furthermore, the case narratives may be relevant for signal assessment, as well as validation. **Proposed change:** Move the following statement to the start of Section IX.C.2.1: "When validation or assessment of a signal is supported by data from EudraVigilance, marketing authorisation holders should take information from the case narratives into account, as applicable."
368		**Comment:** Term "Active substance" does not specify the brand for the MAH. Is the expectation that all products with the same active substances must be reviewed by all MAHs? **Proposed change**: Can it be clarified that each MAH reviews their own products.
IX.C.3.2. and IX.C.3.4.		**Comment:** The concepts signal validation and assessment are mixed up. Variations are required to be submitted within 3 months after signal validation. But, at signal validation it is not clear yet if a label variation is anticipated. This can only be recommended after full assessment of the signal. After the signal validation step the MAH needs to carry out further work on assessing the signal, determine causality, agree core labelling impact and prepare and submit SmPC. Depending on the issue, its priority and complexity, three months for the full assessment may be challenging. **Proposed change:** Change the timeframe to 6 months (or Day 180 of signal).
416-421		**Comment:** First sentence of paragraph is too complex and needs editing because the criteria for notification should be simple and immediately understandable. **Proposed change:** Change wording to "If a validated signal is discussed in the frame of a PSUR within 3 months, a standalone notification is not necessary."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
439		**Comment:** Signal notification as soon as possible and no later than 30 days: depending on the complexity of the signal this timeline may be too tight for MAHs to come to a sound conclusion whether a variation is required because this needs a thorough signal assessment and not just signal validation. **Proposed change:** The module should describe how to handle situations in which the MAH concludes that a variation is needed after the signal notification was sent out.
447		
Lines 477-478 Lines 553-554		
Lines 541-555 (end) Appendix 1, Figures 1-		

4. General comment on GVP Module IX Addendum I

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	The focus of the document is on disproportionality analyses. It would be worthwhile citing the use of other methods such as volcano plots, rate differences or p-values as a way to identify imbalances. These methods should of course only be as an add-on to all other aspects of signal detection. It would be valuable to provide guidance on patient exposure (or surrogate markers thereof) in relation to signal detection strategies.
	Section IX.Addendum.I. Mixes-up terminology and process. For example, the steps in the process of signal management apply universally to all stakeholders and should not be confused with the responsible functions/ bodies for a particular step.
	Section IX. Addendum I.2.2 It would be helpful to include examples to illustrate the requirement to detect signals related to increased ICSR reporting frequency "new aspects of known association including change in the frequency, duration, severity or outcome of an adverse event".

5. Specific comments on GVP Module IX Addendum I

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
35-36		**Proposed change:** Add to the text "To limit the chances of failing to detect a signal" the following "and to detect a spurious finding".
84-85		**Comment:** In the sentence "these ICSRs reflect the background incidence", we suggest to replace "incidence" with "reporting proportions" because disproportionality analysis works with reporting proportions and does not account for event incidence. In disproportionality analysis the incidence denominator (number of treated patients or person-time at risk) is absent and the incidence numerator (the true number of incident cases) is subject to reporting bias. **Proposed change:** "Hence these ICSRs reflect the background ~~incidence~~ reporting proportions of the event in patients receiving any medicine."
87		**Comment:** Line 87 is only true with a large, consistent background reporting. This line should be changed as follows. **Proposed change:** *When an adverse event is caused by a medicine* ***and the database for analysis is sufficiently large and diverse****, it is reasonable to assume that it will be reported more often (above background incidence) and hence this ratio will tend to be greater than one.*
87-88		**Comment:** Because disproportionality measures as contrasts of reporting proportions are not algebraically determined by causal contrasts (defined in terms of event incidence), we suggest removal of the words "above background incidence". **Proposed change:** "When an adverse event is caused by a medicine, it is reasonable to assume that it will be reported more often ~~(above background incidence)~~ and hence this [disproportionality] ratio will tend to be greater than one".
100,102,111		**Comment:** Performance of the disproportionality analyses is used interchangeably with the performance of the signal detection system. As the statistical signal detection and the signal detection system may include components other than disproportionality analysis which have an impact on the overall performance of the signal detection system. **Proposed change:** We suggest that the specified terms are not used interchangeably.
Line 103:		**Comment:** This definition of sensitivity is common for pharmacovigilance, but is different from the notion of sensitivity

		in the broader statistics/diagnostic testing field. Suggest line 103 is modified as below. **Proposed change:** *1. High sensitivity, defined as the proportion of SDRs* ***~~(the proportion of adverse reactions for which the system produces SDRs);~~***
103-106		**Comment:** Sensitivity and specificity can be assessed by simulations and/or using a retrospective analysis selecting ADRs and AE known not to be associated with the drug. **Proposed change:** The Agency should comment in this section about high specificity as it could also be important e.g. low false positive rate.
Reference #7		**Comment:** The first author is missing. **Proposed change :** ***Maciá-Martínez, M,*** *de Abajo, F.J., Roberts, G. et al. Drug Saf (2016) 39: 29. doi:10.1007/s40264-015-0351-3*
146-153		**Comment:** Paragraph does not provide guidance on how to estimate lower confidence bounds and how this relates to a point estimate. **Proposed change:** To provide guidance, or a pointer to where to find guidance, on the above.
160		**Comment:** Definition of threshold is missing. **Proposed change:** Please add a definition of threshold.
194-224		**Comment & request for change:** Although the limitation of not accounting for the overall reporting for this drug is acknowledged, suggest replacement of statistics based on absolute event counts with those for reporting proportions as using the reporting proportion instead of the absolute count would be more appropriate.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<10/10/2016>

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
EUCROF- Pharmacovigilance Working Group

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

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

Stakeholder number *(To be completed by the Agency)*	General comment
	A. The document issued for the public consultation was not in "track changes" mode that slowed the review process. B. Questions on which the Agency seeks specific feedback by means of the public consultation: 1. Are the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders acceptable (see IX.C.2.1.)? ***Answer:*** No (see below) 2. Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable (see IX.C.2.2.)? ***Answer:*** Yes 3. Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable (see IX.C.3.)? *Answer:* **No (see below)**

4. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 147-152		***Emerging safety issue*** A safety issue considered by a marketing authorisation holder in relation to an authorised medicinal product under its responsibility to require urgent attention of the competent authority because of the potential major impact on the risk-benefit balance of the product and/or on patient or public health, that could warrant prompt regulatory action and communication to patients and healthcare professionals (see also GVP Module VI and IX.C.3.1.). Comment 1: Line 152 contains reference to IX.C.3.1 and in return section IX.C.3.1 contains reference to ESI definition. Circular references should be avoided. Comment2: Definition of ESI has been changed and does not include anymore ESI examples. We think that for clarity purposes previous ESI definition should be reinstalled. Proposed change (if any): ***Emerging safety issue*** Events may occur, which do not fall within the definition of reportable valid ICSRs, and thus are not subject to the reporting requirements, even though they may lead to changes in the known risk-benefit balance of a medicinal product and/or impact on public health. Examples include: • major safety findings from a newly completed non-clinical study; • major safety concerns identified in the course of a non-interventional post-authorisation study or of a clinical trial; • signal of a possible teratogen effect or of significant hazard to public health;

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		• safety issues published in the scientific and medical literature; • safety issues arising from the signal detection activity (see Module IX) or emerging from a new ICSR and which impact on the risk-benefit balance of the medicinal product and/or have implications for public health; • safety issues related to the use outside the terms of the marketing authorisation; • safety issues due to misinformation in the product information; • marketing authorisation withdrawal, non-renewal, revocation or suspension outside the EU for safety-related reasons; • urgent safety restrictions outside the EU; • safety issues in relation to the supply of raw material; • lack of supply of medicines. etc
Line 171 (line 167-172)		Comment: What does 'as appropriate' mean? Is it that 'MAH shall liaise with those collection systems that is likely to receive adverse event reports' or does it mean if and as described in RMP (i.e. assessed necessary/important for future assessment of a risk). Proposed change (if any):
Line 261-262		Comment: Line 261 reads 'In some circumstances, special consideration may be given to signals that may cause media attention and/or public concerns (e.g. adverse events following mass immunisation).' The only 'special consideration' the MAH could take is to give the signal a higher priority. Do lines 261-262 apply to all organisations or are MAHs excluded? Proposed change (if any):

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 317-318		'Each organisation should validate and prioritise signals they have detected (or that have been brought to their attention) Comment: Table IX.1 limits MAHs involvement in signal management to EV monitoring, signal detection and signal validation only. However, lines 317-318 as well as Figure IX.1 stipulate more involvement of the MAH in the signal management. Proposed change (if any): Amend the first line of the list of tasks in the Table IX.1 as follows: Eudravigilance monitoring, signal detection, validation and prioritization.
Lines 328-332		'National competent authorities and the Agency shall cooperate in the monitoring of the data available in the EV database. Marketing authorisation holders shall monitor the data available in the EudraVigilance database to the extent that they have access to the database [IR Art 18 330 (2)]. Such monitoring should be performed to determine whether there are new risks or whether risks have changed and … '. Comment 1: Usually the MAH will not have access to case narratives. However, the monitoring whether risks have changed, that is required from the MAH, involves monitoring of change of frequency/severity/etc. that is part of the case narratives. These cannot be accomplished within the routine MAH access rights. Comment 2: Having the EMA, multiple National Authorities and several MAHs perform the same task of EV monitoring does not appear as the most efficient way of utilizing pharmacovigilance resources. A vast amount of resources could be saved, without jeopardizing the efficiency of EV database monitoring by the EU network, if the EMA only conducted signal detection and the results were communicated to National Competent Authorities and MAHs.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any): Delete corresponding reference to MAH in the lines 329-333, 338-348, 356-359 and in the Table IX.1.
Lines 338 - 348		For marketing authorisation holders, the policy provides the option to request access to case narratives held in EudraVigilance ('ICSR data set level 2B'). Prior to requesting access to case narratives, the following criteria should be met: • The review of the electronic reaction monitoring report suggests a signal (see IX.A.); • To the best of the marketing authorisation holder's knowledge, the signal is not addressed in the product information of any medicinal product authorised in the EU with the concerned active substance (see also IX.C.3.4.); • Based on the information published on the European medicines web-portal (see IX.C.8.), the signal was not recently addressed by (a) competent authority (ies) of (a) Member State(s) or by PRAC. When a signal originates from EudraVigilance data, marketing authorisation holders should review the corresponding case narratives as part of the signal validation. Comment: To save resources only EMA will need to conduct review of the safety data that is kept in the EV database. Proposed change (if any): Examples of when a MAH can request additional access rights should be limited to a scenario when after detecting a signal from any source the MAH finds not sufficient evidence in its internal safety database to validate the signal, which would justify, if applicable, the MAH's access to EV database for case narratives of similar events. Comment 2: Define the used term "electronic reaction monitoring report" in the IX.A.1 section of the module.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 356-359		'Marketing authorisation holders, the national competent authorities and the Agency shall ensure the continuous monitoring of the EudraVigilance database with a frequency proportionate to the identified risk, the potential risks and the need for additional information on medicinal products or active substances' Comment 1: Is it necessary to clarify what 'proportionate' means e.g. 'as specified in the RMP' or similar'? Note that line 374 reads 'Each organisation should document the frequency of their monitoring of EudraVigilance data'. Perhaps this is sufficient clarification. Comment 2: To save resources the monitoring of the database has to be conducted by EMA only and results communicated to MAH. Proposed change (if any): Delete reference to MAH in lines in 329-333, 338-348, 356-359 and in the Table IX.1
Lines 383-386		When a marketing authorisation holder becomes aware of an emerging safety issue (see IX.A.), they should notify it in writing to the relevant competent authority(ies) of Member State(s) and to the Agency to the mailbox "P-PV-emerging-safety-issue@ema.europa.eu". This should be done within 2 working days of becoming aware of the issue. Comment 1: When a marketing authorisation holder becomes aware of an emerging safety issue they should notify it in writing to the relevant competent authority (ies) of Member State(s) and to the Agency. Line 385-386 state that 'This should be done within 2 working days of <u>becoming aware of the issue.</u>' This seems to be in line with the sentence in line 266-267 'Such measures may be required before a formal assessment of the signal is concluded.' It however contradicts the guidance given in

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		• Section 'IX.C.3.3. Periodic safety update report' line 427 'Validated signals requiring urgent attention should be reported as emerging safety issues regardless of the submission date of the PSUR (see IX.C.3.1.).' • Figure IX.1 that illustrates notification options after validation of a signal. Please clarify whether emerging safety issues should be notified within 2 working days of becoming aware of the issue or 2 working days after validation of the signal. Proposed change (if any): Instead of "This should be done within 2 working days of becoming aware of the issue". Insert "This should be done within 2 working days after validating a signal or 2 working days after becoming aware of any other safety issues falling under the definition of ESI". Comment 2: It is not clear what does "…notify it in writing to the relevant competent authority(ies) of Member State(s)…." mean? Which competent authorities should receive this notification for a centrally authorized product? All 28? Proposed change (if any): When a marketing authorisation holder becomes aware of an emerging safety issue (see IX.A.), they should notify it in writing to the relevant competent authority of a rapporteur country for CAP, each national competent authority for DCP/NAP and to the Agency to the mailbox "P-PV-emerging-safety-issue@ema.europa.eu".
Lines 409 - 412		When the application refers to the introduction of a change not reflected in the innovator product information, marketing authorisation holders for generic products should liaise with the relevant competent authorities prior to the submission of such variation application to agree on the appropriate way to handle the potential amendment of the product 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')*
		Comment: The same should apply when the application refers to a variation affecting more than one active substance (class effects). Proposed change (if any): n/a
448-450		Within 30 days of receipt of a validated signal, the PRAC rapporteur or (lead) Member State, as applicable, should confirm or not the signal, i.e. decide whether or not it should undergo PRAC analysis and prioritisation at the subsequent meeting Comment: Figure IX.1 stipulates that the only time when PRAC/MS can follow the above scenario is after receiving safety information through the "standalone signal notification" pathway. All other signal notification pathways seem either as not requiring any signal confirmation (variation, PSUR) or signal confirmation should be done more expeditiously (ESI). Proposed change (if any): Chapter on signal confirmation by Member States (IX.C.4.) should take into account and refer to the reporting pathways (ESI, Variation, PSUR or SSN) when describing processes conducted by PRAC/member states.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual

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

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

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
22-23,	FARMAINDUSTRIA	Comment: Before assessing this, MAH should be informed which data pool should be initially used to initiate the activity of signal detection. Is it expected that MAH will mine safety data from its own database and thereafter consulting Eudravigilance (EV) database to confirm or rule out signals?, or is it expected that MAHs will directly mine data from EV data?. According to line 318 we understand that data from any source should be considered. Hence we propose that narratives might be consulted once MAHs could obtain listings of the cases housed in EV database (i.e listings for the pair drug-event considering population, time to onset, duration of the reaction, dechallenge and rechallenge response, outcome, etc). Proposed change (if any): - Specification of the data to be mined (MAHs database vs. EV database or both). Data pool to initiate the activity.	
27-28, 372-373	FARMAINDUSTRIA	Comment: Frequency of monitoring the Eudravigilance data should be modified since there are different risk levels for each product. Frequency could be enlarged (i.e: one to two year for well-known products), considering that EURD list also establishes extended periods for PSUR presentation.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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): [373] Eudravigilance data should not exceed XXX months. (12,18,24....)	
29-30	FARMAINDUSTRIA	Comment: Modalities for communication of emerging safety issues (ESI) and validated signals are not clear enough. MAHs would like to be clarified content and format of ESI and stand alone single notification. Further, MAHs would like to be clarified if –in case of a variation application submission - there will be requested the internal signal validation report during. In general terms, MAHs would like to know the report type, format and content required for providing each type of safety communication once the concerned signal is validated. Proposed change (if any):	
317, 326	FARMAINDUSTRIA	Comment: If MAHS has to prioritise also the signals, this activity should be listed also for them in table IX.1 (line 326) Proposed change (if any): Table IX.1 should be amended.	
331	FARMAINDUSTRIA	Comment: MAHs should monitor into the EV database for confirming or ruling out its owns signals (new risks, risks change, or other impact on the risk-benefit balance). Proposed change (if any):Such monitoring 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)*
		performed to confirm or rule out prior detected new risks or [...332] OR specify exactly what is expected from National competent authorities and what is expected from MAHs side.	
385-386	FARMAINDUSTRIA	Comment: Emerging safety issue (ESI) should be validated as such. Although we agree to send the ESI in 2 working days, we would like to clarifiy that this due date will be calculated after the date when ESI is validated (since is included in section IX.C.3 for signals validated by the MAH in the EU) Proposed change (if any): This should be done within 2 working days of validating such signal as emerging safety issue.	
451	FARMAINDUSTRIA	Comment: When a Member State decides not to bring a validated signal for discussion at PRAC, this decission should be communicated to MAHs (in order to allow them to track the outcome of each submitted signal) Proposed change (if any):	
	FARMAINDUSTRIA	Comment: We do not see in the GVP module IX any reference to the detection of signals in cases coming from social media. Do you think that we should have any special consideration when assessing these cases? Should they be treated	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To 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)*
		separately / do they have the same value as the rest of spontaneous reports? Along these lines, at the moment of detecting a signal, do you consider that spontaneous cases reported by consumers have also the same value as those reported by HCPs? Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
Gilead Sciences International Ltd

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	This module appears to be written almost exclusively from the viewpoint of the regulatory authority and this makes the interpretation for where the MAHs fit into the process and can fulfil their responsibilities somewhat difficult to understand. It seems that MAH are only there to detect signals, then send a validated signal to the regulators and the entire assessment and prioritisation through to action is a regulatory authority activity. The MAH should be active themselves in the critical steps after initial signal validation and it seems to me that this is contrary to the responsibilities the MAH has. E.g.: • Line 122-130: Signal confirmation - This definition now solely refers to actions by regulatory authorities – is the MAH not needed for signal confirmation? • Line 131-136: Signal assessment and prioritisation - Again, the definition only considers the actions by the PRAC – the MAH appears to be absent from this critical step. • Line 326 Table IX.1: Clearly disempowers MAHs after initial signal detection and Eudravigilance monitoring. At the same time, there appears to be a lot of duplicative effort in this step.

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')*
29		Comment: The proposed timeline of 3 months is insufficient for the signal to be assessed and a variation to be prepared. Proposed change (if any):
122 - 146		Comment: The definitions all seem to be from the perspective of the PRAC/regulators. There is no indication of MAH activity for signal confirmation or signal analysis. Suggest to also reflect the MAH processes within explanations. Proposed change (if any):
147 - 152		Comment: The difference between emerging safety issue and signal is unclear. Proposed change (if any):
163 - 164		Comment: Sentence suggests that signals may be detected from RMP updates. This is somewhat difficult to understand from the perspective of an MAH, as RMPs should be updated once relevant knowledge is acquired and therefore one would expect that no new signals could be detected, rather that the ultimate outcome of a detected signal may result in an RMP update, once it has been recognised to be an important identified or potential risk or key missing information. Proposed change (if any):
176 - 187		Comment: Section appears somewhat superfluous to the following detail that is much more useful and clear

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		from Line 188 onwards. Proposed change (if any):
184		Comment: It is unclear who performs the activity and who needs to document it. Proposed change (if any):
290 - 292		Comment: Here the MAH appears to be taken as the relevant party subject to the requirements outlined in the previous paragraphs – this however is the first time that it appears clear that the MAH has a fundamental role beyond initial signal detection. Overall, more clarification is needed for the role and responsibility in each step of signal management for both regulators and MAHs from detection through final action. Proposed change (if any):
317 - 318 and 326 Table IX.1		Comment: MAHs are not processing signals per this table. The MAH should have responsibility for signal analysis and assessment. If this table (and some of the definitions in previous section) is specific to signals originating/detected by the EMA then suggest it to be clear in the guidance. Does this signify that there will be expectation for duplication of effort? Proposed change (if any):
329 - 330		Comment: As it is recognised that MAHs have limited access to Eudravigilance, would it be generating less redundancy, if the Agency as to date takes the prime responsibility for monitoring of Eudravigilance and MAHs are informed of signals detected therein, rather than being expected to also perform monitoring on a limited access dataset, which will by force reduce the interpretability of anything that is being reviewed.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any):
338 - 348		Comment: As above, this seems an overly complicated and burdensome activity that would become unnecessary, if the responsibility for Eudravigilance signal detection remained with the agency. If signal validation is the first opportunity to review individual case narratives, a lot of spurious blips may require access requests and may impact adversely on effective and efficient processes for true signal validation. Proposed change (if any):
345 - 346		Comment: Do MAHs need to monitor this web-portal regularly as well? Proposed change (if any):
368		Comment: A routine two week interval for monitoring for additional monitoring products may be too short, particularly where exposure is low (e.g. in the case of orphan products) – a more flexible interval setting should be allowed with appropriate rationale and review of interval appropriateness. Proposed change (if any):
376 - 381		Comment: Timelines in this section are confusing and it appears that there are several options that up to now didn't appear relevant when the currently proposed activity for MAH to only go through from signal detection to validation are considered. Overall clarification of the reporting options and associated timelines are needed. Proposed change (if any):
388		Comment: Clarify that within 2 working days there is usually no complete documentation available and therefore the wording should take account of the situation by stating 'all available documentation' which

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		may/will be supplemented as soon as possible. Proposed change (if any):
401		Comment: Validation is only the confirmation that additional review is needed, it is not the agreement that a causal association exists. Consideration of label updates or changes to RMP should not be made at validation. Proposed change (if any): "When, as a result of *signal assessment*,…"
404 and 416-421		Comment: 3 months seems short to work-up and decide on PI updates following validation (also does this mean you file an SmPC update with the PSUR?) Proposed change (if any):
406 and 418		Comment: It is confusing that we may not have to report a validated signal, if we have sufficient information to start a variation, which will then have to be submitted within three months. Signal validation should not be a full evaluation and assessment of the signal and thus it is difficult to understand what the expectations on the MAH are on evaluating a signal at validation stage. Proposed change (if any):
434 - 446		Comment: It is not clear here if the MAH sends notification that a signal has been validated, or if the complete signal assessment should be included within 30 days. The MAH would not know if an RMP or label update is required until after the signal assessment and it would not be feasible for this to be achieved within 30 days. 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')*
439		Comment: This may create confusion ie. MAHs following their internal timelines for signal work-up and in parallel PRAC following their process which have different timelines/milestones (as described within). Proposed change (if any):
447 - 463		Comment: The conditions under which a validated signals are not proposed for PRAC considerations are conflicting with the understanding of what constitutes a validated signal and the signal confirmation step appears ill-defined and the role of the MAH is completely absent. Proposed change (if any):
448 - 450		Comment: Does this include the ones received from MAHs? Proposed change (if any):
474 - 482		Comment: Suggest there needs to be clarity on the process for signals origination from EMA/MSs vs MAHs, will all signals be processed via this route and these timelines? Proposed change (if any):
477 - 478		Comment: MAHs should collaborate with the PRAC for the assessment of the signals by providing the additional information requested. This suggests that there is a role and expectation on the MAH on the assessment of signals, which has not been articulated in the previous pages. It is necessary to clarify the ongoing MAH work expectations in the earlier sections. 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')*
547 - Figure IX.2		Comment: Figure does not acknowledge that the MAH may be assessing the validated signal independently, as they have global obligations. Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
[redacted] Guild of Healthcare Pharmacists

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1. General comments

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

The Guild of Healthcare Pharmacists (GHP) supports the proposed changes made in this major revision.

Questions on which the Agency seeks specific feedback by means of the public consultation:

1. Are the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders acceptable?

Yes
However, we feel that staff members within national competent authorities and marketing authorisation holders must (rather than 'should') be fully familiar with the training materials made available by the agency

2. Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable?

Yes, the recommendations seem to be realistic

3. Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable?

Yes

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 213-214		**Comment:** We feel that 'Abuse' and ' Falsified medicines' should be included **Proposed change**: Line should read: Reactions occurring in different patterns of use (e.g. overdose, misuse, **abuse**, off-label use, medication errors and **falsified medicines i.e. a medicinal product with a false representation of its identity or its source**
Line 293		**Comment:** We feel that staff members within national competent authorities and marketing authorisation holders must (rather than 'should') be fully familiar with the training materials made available by the agency **Proposed change:** Staff members **must** be specifically trained in signal management activities in accordance with their roles and responsibilities (see GVP Module I).
351-354		**Comment:** As above, staff members must be suitably trained **Proposed change:** Relevant staff members within national competent authorities and marketing authorisation holders **must** familiarise themselves with the training materials made available online by the Agency on EVDAS and the training **must** be documented in line with the organisation's internal procedures

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<October 11th, 2016>

Our reference: [redacted]

Draft guideline on good pharmacovigilance practices (GVP) Module IX - Signal management (Rev. 1) (EMA/827661/2011)

Comments from:

Name of organisation or individual
International Plasma Fractionation Association (IPFA) Our reference: [redacted]

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	1. Are the proposed criteria for access to case narratives held in EudraVigilance by marketing 22 authorisation holders acceptable (see IX.C.2.1.)? It is difficult to give specific feedback as the MAHs are not aware of what exactly will be available in this new version of EV database/process. How easy will it be to access and interpret? It is unclear which kind of narrative could be available in Eudravigilance and not in the MAH pharmacovigilance database. Does this means that for signal detection activity the MAH should only take into account the EV database (and not the MAH database)? if yes, why ? if no please clarify +++. Will the electronic reaction monitoring report be available for each single product ? How often ? How will it be accessible? will the MAH receive alert when such a report will be available ? What will be its format ? The scenario of an increased frequency of an excepted adverse drug reaction seems not to be covered.

	2. Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable (see IX.C.2.2.)? The MAHs have not any clear view of what the activity of monitoring of Eudravigilance data really imply? How long will it take ? what will be the link between this monitoring and the electronic reaction monitoring report ? What about the monitoring in the MAH database ? Biologics/plasma derived products are included by default in the additional monitoring list even if no additional pharmacovigilance activities or risk minimisation activities are requested. A 2 weeks interval does not seem appropriate for all those product. This should be correlate to the amount of ICSRs received with the product per week/month/year.
	3. Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable (see IX.C.3.)? Timelines for communication of emerging safety issues are clear (would be preferable to call them emerging urgent safety issues). The modalities could be more precise (especially what information should be provided ? is there any form to fill in ?) It is unclear if an emerging safety issue is always a validated signal ? depending on the response it would maybe good to have a section IX.C.3.2 validated signals and then the 3 different scenario in 3 subsections. Concerning the scenario where a variation of the term of the MA is needed and the link with PSUR should be clarify together with figure IX.1. The figure seems to say that there is no need to submit a variation if there is a PSUSA within 3 months. It is not so clear in the sections IX.C.3.2 and IX.3.3. Concerning the timelines for validated signal it would be good to take into account the seriousness of the adverse reaction. If non serious, the reporting in PSUR could be enough. Similarly, it should be mention that variation of the term of MA should be submitted within 3 months in case of serious ADR.

	The link between signal and risk (potential or identify) should be explain/explicit

4. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
117-121		Comment: It would be good to clarify what is considered a sufficient evidence to justify further analysis of the signal. Proposed change (if any): The process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence about the potential causal relationship to justify further analysis of the signal by the Competent Authorities [IR Art 21(1)]. This evaluation should take into account the strength of the evidence, the clinical relevance and the ~~120~~ previous awareness of the association (see IX.B.3.).
161-166		Comment: only signal from spontaneous reports are described it would be good to described what should be done with information from clinical trials.
188		Comment: the title of section IX.B.3 should be signal validation (or at least should contain this term) to better understand where we are in the signal management process.
235-245		Comment: Would be good to explain when the signal could be considered as validated. Would be good to explain the link between an signal and a risk (potential/identified) vs module V Proposed change (if any):
265		Comment: It would be good to explicit the link between signal and risk

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed change (if any):
341		Comment: what is exactly the electronic reaction monitoring report ? who is doing it ?
342-344		Comment: what about biologics? Proposed change (if any):
347-348		Comment: need to be clarified
398-399		Comment: EMS = validated signals that cannot wait up to 30 days for confirmation by MS. It is not clear in the definition (lines 148-152) that EMS should be a validated signal. In the definition the emergency is such that the MAH has maybe not yet totally validated it. This should be clarified +++. What does really means "that cannot wait up to 30 days for confirmation by MS" ? it cannot wait 30 days to be communicated to the CA neither. Proposed change (if any):
401-405		Comment: does this means that the variation will be submitted without any review by the PRAC before ? Please see also response to specific questions at the top of the document Proposed change (if any):
420-421		Comment: when does the MAH have to consider that the variation needs supportive data ? please precise.
435-436		Comment: would be interesting to know what kind and level of information will be requested to report a signal to be able to evaluate the workload generated by this activity (form template)
439		Comment: why this could wait 3 months in case of PSUR and here should be done within 30 days ?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
455-456		Comment: the SPC of other products should be easily available in the EMA website
541		Comment: the left part of the figure should be clarified +++

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

October 10, 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
CBG-MEB

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Terminology: The definitions of prioritization and assessment as self-standing processes, not only in relation to PRAC should also be defined in this section., in line with what is mentioned further on in section IX.B.4 The definition of Emerging safety issues is still to vague for stakeholders to understand when an issue is a ESI or just a signal. Can this be clarified? In relation to a signal especially, for example – very urgent signals which should be handled in less than 30 days. The Role of Rapporteur can also be defined.
	Section IX.B.3 Evaluation of the evidence supporting a signal: The bullet point of previous awareness could be moved to the first place (instead of being in third place), as this would follow a more logical order when evaluating a detected signal (i.e. starting by checking if the event is already reflected in the SmPC of the medicinal product).
	IX.C.2.2 Periodicity of monitoring: We think this is now well addressed and clear. Another factor to be considered might be: recent media attention or public concerns regarding the product or a recent referral.
	In general, we consider that the new draft does not clearly reflect other sources of signal detection besides ICSRs (e.g. section IX.B.3 "Evaluation of the evidence supporting a signal" should also reflect that a signal can be identified in literature). We consider that section IX.B.3 should either specify that it addresses only signals identified in ICSRs or be expanded to include elements to be considered when evaluating the evidence of a signal detected in literature or other sources.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 123-126		Comment: The role of the Member state / PRAC Rapporteur in the definition of signal confirmation could be moved to a second sentence for clarity of the definition. Proposed change (if any): "The process of deciding whether or not a validated signal should be analysed and prioritised by the PRAC at the subsequent meeting. It should be performed by the (lead) Member State or PRAC Rapporteur, as applicable, within 30 days from the receipt of the validated signal." Comment: Product authorised in accordance to the DIR and in accordance to REG (e.g., nationally approved and Centrally approved). This way of definition might confuse some stakeholders, especially since later in the document, CAP and NAP are used. Proposed change (if any): replace with nationally approved products and centrally approved products. (and explain in a footnote what they exactly mean)
Lines 137		Comment: It could be better explained that the PRAC appoints a Rapporteur, as the signal assessment is not done by PRAC but by Rapporteur and PRAC is involved in the decision making. Suggest to change the title to reflect this. Proposed change (if any):
Line 204		Number of cases in context of the exposure can be moved on second place bullet, after number of cases, since they are related.
Line 225		Additional sources of information may provide further evidence ~~on~~ **for or against** the association,
Line 321		It could be further explained that if the signal has been validated by a Marketing Authorisation Holder, the Agency will allocate a (relevant) Member State where the substance is authorised for confirmation (as shown in Figure IX.2)
Line 326, table		Do the roles and responsibilities as mentioned in the first line ('EudraVigilance monitoring, signal detection and

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
IX.1		validation') only apply to signals based on EV data? Responsibilities may be different based on the source, e.g. MAHs should also monitor their own database (next to the EV database) and literature. For the validation step: the organisation who detects a signal will also validate it (regardless of your official responsibility as a Rap, Lead Member State, etc.
Line 338		Please add "in the context of signal management' here, as the EudraVigilance Access Policy also allows access to case narratives in the context of other pharmacovigilance assessments.
Line 364		**(Extent of)** patient exposure
Line 394		Please clarify if this means that all ESIs will be discussed at the level of the IRN?
Line 504		According to Art 22 (Reg 1234/2008) an Urgent Safety Restriction can also be initiated by a MAH. The difference between an USR and an ESI needs to be better explained.
Line 547 and 549		Figure IX.2 and figure IX.3: will the justification for non-confirmation also be shared with the MAHs?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14-Oct-2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
medac GmbH

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

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

Stakeholder number *(To be completed by the Agency)*	General comment
	Questions on which the Agency seeks specific feedback by means of the public consultation: **1. Are the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders acceptable (see IX.C.2.1.)?** ***These criteria have been developed to prevent unjustified download of case narratives, in relation to Annex C (Confidentiality Undertaking for Marketing Authorisation Holders) of the EudraVigilance Access Policy which aims at ensuring the protection of personal data.*** Overall, the proposed criteria for access to case narratives are acceptable. However, it should also be taken into account that indication of a potential signal may also arise from other sources than electronic reaction monitoring, e.g. aggregated data published in the scientific literature or published case reports which for any reason have not been entered into EudraVigilance. Therefore it would be helpful if additional access criteria than electronic reaction monitoring would permit MAHs to read case narratives. **2. Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable (see IX.C.2.2.)?** In general, the recommendations regarding the frequency of monitoring is acceptable, i.e. a 2 weeks' interval for active substances in medicinal products included in the additional monitoring list and an interval not exceeding 6 months for other active substances, based on their respective risk profile. **3. Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable (see IX.C.3.)?** Overall, the proposed modalities for communication of emerging safety issues and validated signal by MAHs are acceptable. However, the timelines for communication of emerging safety issues are quite short if extensive documentation needs to be

Stakeholder number *(To be completed by the Agency)*	General comment
	submitted. We would therefore propose to notify the Agency within two working days after detection of the ESI with all relevant information available at that time. If extensive research has to be performed and complete data cannot be submitted within two working days a longer time frame for submission of further documentation should apply. The timelines for communication of validated signals are acceptable. However, with regard to IX.C.3.3., it would be helpful if further clarification could be provided as to when a signal with any potentially related amendment of the product information should be notified within a PSUR and when a variation should be submitted, unless this is at the sole discretion of the MAH and both possibilities are considered equally acceptable. Furthermore, it would be helpful to specify the modalities of submitting proposed changes to product information within the PSUR.

2. Specific comments on text

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

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
Medicines for Europe Contact: [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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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Medicines for Europe welcomes this opportunity to comment and contribute in this major revision of the GVP Module IX. The revision reflects experience gained over the past years. A structured, detailed guidance is providing some clarity on important aspect of roles, responsibilities and terminologies for signal management process. Also, the provision of flowcharts is considered very helpful within the process of signal management.
	However, the process as outlined within the revised GVP IX module **seems to imply a multiplication of signal detection activities** as EMA, NCA and MAHs will perform signal detection on the EudraVigilance database. This multiplication and signal detection efforts of each MAH on the same dataset of EudraVigilance leads to duplication and **increased heterogeneity and number of signals as MAHs use different methodology, standards and thresholds**. MAHs with a limited number of ICSRs reported to EV will need to perform signal activities on non-company data, which were already assessed by other stakeholders, posing duplication of work on these generic companies and leading to increased numbers of heterogeneous signals the Agency will have to address and process in due time.
	In view of these issues the following pragmatic approach would be proposed: MAHs should be responsible for the signal detection process related to their own products in their own database to which they can upload relevant cases from the authorities on their potential signals of their products. This seems to be appropriate as generic companies share the same data and even more available information as e.g. narratives are available within the MAHs database and there is no need not to be separately requested.
	Across the module there is an underlying assumption over the data sources to screen for new signals (as a justification to multiply the search) but in principle both MAH and Competent Authorities have the same set of data to look into, as well as equal access to it. All MAH are obliged to report all ICSR, and also to publish all the studies performed. Therefore the overlapping of sources seems not to provide an added value to the signal detection process. We would consider more appropriate to **identify areas of synergy in order to avoid duplication of efforts in data sources for signal detection.** As an example, we would propose the MAH to search into own pre-published data, experimental data sets, if relevant, and the Competent Authority searching in already reported and published data sets. In conclusion, complementary signal

Stakeholder number *(To be completed by the Agency)*	General comment
	detection would be preferable, rather than a duplication of processes, which is against the intention of the legislation.
	Taking into account the expected huge amount of requests for discussion of validated signals at the competent authority side due to notifications of MAHs´ EV individual repeated signal detection processes, it is foreseen that this might delay or even block the process of signal management as outlined within the current GVP IX revision document.. The MAHs agree to have their product information updated with the most up to date scientific knowledge. However, as there is no harmonisation of product informations across the various CAs and no joint tool, or system to access up-to date product informations nor alert system in case of product information update, the MAHs lack overview over current product informations. In practice, it seems we are far from manage to identify the relevant up-to date product informations needed for complying with the current proposed process across the EU, as we lack the proper references, processes and tools to do it nimbly. So for example, some EU Competent Authorities (AEMPS) have electronic tools to fractionate the product information content of different MAH, but the MAH seem to miss the global overview of the content (only pdf documents available, without clear identification of last update date). We would like to emphasize the fact that product information differs depending on countries, leaving the MAHs with the challenge of selecting the most appropriate reference or interpretation of differing wording. Therefore, harmonisation across Europe should be emphasized, starting with the approval process.
	Additionally, in our opinion the process of triggering a variation over the product information related to a validated signal would be better lead by the Competent Authority (CA), as the overseeing entity to define and limit the content of the text to be included. The MAH can then be invited to organise a worksharing to handle the SmPC update after agreement on the updated text with CA. As there is a lead member state foreseen for non-centralised products, it would be acknowledged to be provided with a complete list of CAs responsible for a product.
	We would encourage EMA to provide more guidance to MAHs with regard to the process that triggers MAHs notification of CAs and with regard of the processes that are expected to be done by the MAH and which are not (e.g. extent of Signal assessment within signal validation). Considering the major changes in the process, we believe clarification and guidance to be followed by all MAHs would add to the process of signal management and align the processes at MAHs' end in line with agency's expectation.

Stakeholder number *(To be completed by the Agency)*	General comment
	In addition, it might be worth considering to clarify the connection between the following terms: ongoing signal, closely monitoring topic and potential risk.
	In terms of definitional clarity, a consistency is requested regarding the following terms: signal detection, signal validation, signal confirmation, signal analysis, signal prioritization, and signal assessment. These terms are employed inconsistently throughout the guidance (compare, for example, Table IX.1—referencing all of the aforementioned terms, and corresponding responsibility—to Section IX.B, which excludes signal confirmation and signal assessment). Further, the scope of Section IX.B.3, *Evaluation of the evidence supporting the signal*, is unclear (i.e., does this apply only to signal validation?). Accordingly, we request that EMA consistently employ these terms throughout the guidance. Moreover, please consider including terminology used in other GVP module to provide clear understanding especially with GVP module VII- Periodic Safety Update Report.
	It is recommended that the other supportive guidance documents which are referred in GVP module IX (Rev 1) are finalised prior to finalisation of the module. This would help industry to have a holistic picture and to fully understand expectations from the agency so that required resources can be made available and organisations are ready when module becomes effective. Some of the referred documents which are yet to be finalised are: - Screening of adverse drug reactions in EudraVigilance; - EVDAS report manual and MAH's level 1 access via EVDAS.
	Scenario and example of potential process from MAH point of view: Within the GVP IX, it is outlined in C.3.2. that "marketing authorisation holders should liaise with the relevant CA prior to the submission of such variation application to agree on the appropriate way to handle the potential amendment" after signal validation.

Stakeholder number *(To be completed by the Agency)*	General comment
	In C.3.4. it is stated that standalone signal notification should be completed and sent to the Agency and NCAs. In view of MAHs with small portfolio and limited resources and professional expertise as well as qualification, it is expected that a high volume of requests will be sent to the CAs to comply with the requirements as outlined in GVP IX. It seems practical for MAHs to send such requests for clarification on potential signals to the relevant CAs and the Agency for each of their substance to seek advice on signal validation. In addition, each MAH responsible for generic substances as e.g. Paracetamol, will be sending similar requests, thus the NCAs and Agency are expected to receive a high volume workload to respond to each MAH individually. MAHs with high volume portfolio might also adhere to this approach not to miss signals on EV as well as to economize foreseeable additional costs and FTEs in future doubling their efforts on signal detection adhering to the need of doing signal detection on their own and EV data.
	Questions on which the Agency seeks specific feedback by means of the public consultation: **1.** Are the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders acceptable (see IX.C.2.1.)? *These criteria have been developed to prevent unjustified download of case narratives, in relation to Annex C (Confidentiality Undertaking for Marketing Authorisation Holders) of the EudraVigilance Access Policy[1] which aims at ensuring the protection of personal data.* **Medicines for Europe response:** The process on MAH requesting narratives held in EudraVigilance seems to be challenging. With regard to signal detection, for further analysis of the signal, narratives are a pre-requisite for signal validation. Therefore the suggested approach seems not to be acceptable to guarantee efficient and high-quality signal management by MAHs. It is suggested to facilitate access to case narratives held in EudraVigilance for MAHs so that MAHs can comply with provisions and timelines as outlined in GVP IX. The access to the narratives should be granted without need for requesting for the relevant staff involved in signal validation according to the" European Medicines Agency policy on access to EudraVigilance data for medicinal products for human, Revised Dec 2015, to avoid time delay and extensive bureaucracy work with regard to narrative requests at agency and MAH side. There might be situations where the signal is included in other EU labels but the generic MAH has not enough data to sustain causality/submit safety variations. In this situation, access to case narratives seems to be crucial and should be granted promptly. It is mentioned that when a signal originates from 'EudraVigilance Data', MAH should review the corresponding case narratives. Does it mean that case narrative review from EudraVigilance is not expected for signals originating from MAH's own data? If yes, then it is not aligned with what is mentioned in row 230-231. If no, then it is recommended to clarify the same in guidance.

Stakeholder number *(To be completed by the Agency)*	General comment
	2. Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable (see IX.C.2.2.)? **Medicines for Europe response:** For generic, well established products, the recommendations seem not to be acceptable. There are several objections to the suggested frequencies of monitoring EV data. Six months could be a short period for substances for which only few cases are received and/or there is a well-established safety profile. Therefore, we propose an extension of the periodicity up to 1 year for generic products with well-established safety profile (e.g. generic products for which PSUR is not required). In addition, the suggested timings may impose significant work load on generic MAHs without automated data analysis systems, e.g. every two weeks for actives under additional monitoring. **3.** Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable (see IX.C.3.)? **Medicines for Europe response:** Firstly, the terminology and process expected with regard to signal validation should be clearer and aligned within the document, as raised already above. Furthermore, several questions arose that reveal this section being not fully clear and understood. E.g. it should be clarified the scope of this process, e.g. if this process only refers to signals emerging from the monitoring of EV only, or to all signals detected by MAHs? In case of an emerging safety issue, relevant competent Authorities of Member States and the Agency should be notified within 2 working days of becoming aware of the issue. This time seems to be challenging in view of signal validation, and assessment to MAHs, which is a pre-requisite to forward relevant information to the Agency and not to saturate the system by transmitting less urgent information. Also taking into account the need of requesting narratives as outlined in GVP IX.C.2.1 which seems to be potentially time-consuming. It is suggested to re-consider time frames in view of the need for generic companies to gather sufficient information to comply with the process of not saturate the system by transmitting less urgent information as outlined in IX.C.3.1, which is acknowledged. In addition, the term of "relevant Member States" should be clearly defined (e.g. approved MAs, ongoing MA, Lead MS, MAH has no

Stakeholder number *(To be completed by the Agency)*	General comment
	approved MA in the relevant country). Also, it would be appreciated to receive a dedicated email address for all national competent authorities to receive emerging safety issue notifications. It is outlined that variation should be submitted as soon as possible after a signal is validated but no later than 3 months after signal validations. Signal validation is defined in 117-121 as" signal validation is the process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence to justify further analysis of the signal…" which seem not to include the supporting evidence for assessment and propose actions as outlined in 401. It is also not considered consistent that changes to the product information should be proposed after validation. Therefore, it is proposed to extend the deadline for submission of safety variations up to 6 months for signals that qualify as non-important risks. This would allow more flexibility and synchronization with PSUR submissions. Also, it is suggested to review and adapt terminology to be aligned within the document. It is proposed to use signal evaluation/assessment. It should be noted that notification to relevant competent authority in case of missing information within the innovator SmPC is expected of numerous generic MAHs, leading to huge amount of requests for discussion at the relevant competent authority. This potentially may delay the process. It is proposed that MAHs should only use EV for evaluation of their own signals and rely on the signal detection process by EMA/MS for EV signals. It is proposed to liaise with the relevant competent authority in case the proposed change is not reflected in the innovator product information. Clarification is needed for the situation when the signal is included in another generic SmPC but not in the innovator´s. Also in case there is no innovator available advice should be given, e.g. what generic SmPC can be considered as reference instead. In addition, clarification about "relevant competent authorities" and contact details would be appreciated. Moreover, time frame for liaison with competent authority is not clearly stated. It is stated that that validated signals for which there is sufficient evidence to propose changes to product information and/or RMP shall be included in PSUR, unless the MAH considers that a variation application should be submitted. Clarification or an example about this situation would be appreciable for MAHs to have clear guideline. Also, it is suggested to extend the timeline of due PSUR submission to the following 6 months after signal validation and assessment to allow more flexibility and synchronisation with PSUR submission. It is mentioned that… all validated signals and emerging safety issues …should be reported in the PSUR.' PSUR requires discussion of closed signals too, hence it is recommended that the sentence is reworded to avoid subjective interpretation.

Stakeholder number *(To be completed by the Agency)*	General comment
	Timelines and process how member states and agency come back to the MAH who raised the signal is missing.

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')*
102-103		Comment: It is stated that "only signals related to an adverse reaction shall be considered". From the previous definition, it is not completely clear if this also includes new aspects of a known association (as changes in frequency, duration, severity or outcome) of already known Adverse Reaction. Signal detection approach might differ substantially depending on expectations of detecting new Adverse Reactions or, in addition, new aspects of known associations. Proposed change: To clarify exactly the scope of signal detection in EV only referring to new ADRs or also to new aspects of a known association.
141-144		Comment: Signal detection of member states is explained. It is acknowledged that EV signal detection will be done by a lead member state, thus avoiding duplication and reducing workload in other countries. However, as it is understood, each MAH is in charge of performing signal detection. Proposed change: Please see above as outlined in "general comment". It is proposed that each MAH should be responsible for signal detection process related to its own products using its own database, performing signal detection on own data and using EV for further validation/evaluation of a potential signal.
147		Comment: Examples previously outlined in GVP VI.C.2.2.6 "Emerging Safety Issues" were deleted from the current Module VI revised version. These examples are very useful and guidance for stakeholders and therefor it is suggested to add these in the current revised Module IX, section "Emerging Safety Issue"in IX.A.1. Proposed change: Adding examples previously outlined in GVP IV to "Emerging Safety Issue" of GVP IX

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
155-160		Comment: In case of signal validation, evaluation, confirmation and assessment, the MAH´s evaluation is proposed to be supported by EV data. With this regard, the eRMR are acknowledged to serve as to be supportive to signal detection activities. In MAHs confirming the signal based on own and EV data, the process as outlined in GVP IX.C.3. should be followed. Furthermore, the extend of signal detection activities in EV for post-marketing phase to be performed by generic MAHs should be tailored to signal validation and evaluation of potential signals detected on the MAH´s data. Also, it should be clearly defined which data the MAHs are expected to perform signal detection activities (e.g. clinical trial data).
188		Comment: It is not clear if this section refers to MAH´s process of signal validation or to PRAC processes. Clarification would be welcome.
238		Comment: This section refers to closing signals for which there is not enough data available to support a causal relationship. As closing per se might imply different meanings, it is suggested to be clearer on these signals using "refuted" additionally. Using "refuted" would reflect that the signal was evaluated but insufficient evidence was collected to promote the signal to a risk. Proposed change: closing **and refute** the signal
241		Comment: Some guidance about the understanding of "appropriate time intervals" for monitoring would be helpful (e.g. until next periodic report). Also, monitoring is not mentioned in the flowcharts provided at the end of the document.
244		Comment: In the case outlined here, the signal is closed (and promoted to a risk), as "variation procedure" is not rationale on an "ongoing signal" and variation will be based on PRAC recommendation, as proposed by 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')*
		current GVP IX.
246		Comment: It is clear from section IX.C.1 Table IX.1 that signal prioritisation is the responsibility of PRAC and rapporteur appointed to assess the signal, however it is recommended that Signal Prioritisation section IX.B.4 also suggests MAH as a responsible party for same, in a scenario where multiple signals are identified by MAH at same time. The criteria used in this section should be used by MAH to prioritise the signal when it identifies multiple signals and prioritisation is required.
261-262		Comment: It is not further explained what is expected in case of circumstances of signals that may cause media attention or public concern. Proposed change: To clearly state what is expected in case of signals connected to media attention or public concern. Also to define if it is expected from MAHs to anticipate such signals in certain situations/products or how to react in case media attention occurs due to certain public attention. The expectations e.g. special analysis, increased signal detection frequency should be outlined and the steps of investigation of such potentially artificial signals from the media (which arose e.g. after a new launch of a generic product or a recent scientific publication related to a safety aspect) should be depicted to keep patient safety at the highest level and avoid distrust in medicinal products, pharmaceutical companies and health authorities.
274-275		Comment: It is recommended that even the RATIONALE for method and periodicity of signal detection activities are documented by MAH. It is understood that every MAH will have their quality and documentation system, however it is requested to agency to clarify if it would like to see this rationale documented in any specific type of document. E.g. SOP or PSMF etc.
277-279		Comment: It is suggested in revised module IX that performance indicator of this process should be presented in

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		the PSMF. Further guidance or example on what can be considered as performance indicator would be appreciated.
307-316		Comment: It is mentioned in revised GVP module IX that "All member states shall remain responsible for monitoring the data in EudraVigilance database …" We believe that it's duplication of efforts and as the responsibilities are very clear this paragraph can be rephrased as below. Proposed change (if any): In accordance with DIR Art 107h(1)(c) and Art 107h(3) [IR Art 22(4)], all member states shall remain responsible for monitoring the data in the EudraVigilance, however within the EU regulatory network, the agency takes the lead for EudraVigilance monitoring of active substances contained in at least one centrally……A co-leader may also be appointed to assist the lead member state in the fulfilment of its tasks (IR Art 22(1)].
317-318		Comment: It is stated that each organisation should validate and prioritise signals they have detected from any source, including EV. With regard to signal detection in EV, please see above section "general comment"
326		Comment: The table is helpful but confusing as it defines "EudraVigilance monitoring, signal detection, validation" as roles and responsibilities for MAHs and their products. According to the definition of "Signal validation" in 117-121, signal validation is the process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence to justify further analysis of the signal…".With regard to 347-348 "MAH should review the corresponding case narratives as part of the signal validation". It is confusing as MAHs are required to do validation only - case narratives should not be part of the validation but evaluation process.
329-330		Comment: GVP mentions "Marketing authorisation holders shall monitor the data available in the EudraVigilance

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		database to the extent that they have access to the database." It is recommended that the guidance document related to screening of EudraVigilance is released for consultation prior to making revised GVP module IX effective.
338-340		Comment: The process on MAH requesting narratives held in EudraVigilance seems to be challenging. With regard to signal detection, for further analysis of the signal, narratives are a pre-requisite for signal validation. Proposed change: To facilitate access to case narratives held in EudraVigilance for MAHs so that MAHs can comply with provisions and timelines as outlined in GVP IX. The access to the narratives should be granted without need for requesting for the relevant staff involved in signal validation according to the" European Medicines Agency policy on access to EudraVigilance data for medicinal products for human, Revised Dec 2015, to avoid time delay and extensive bureaucracy work with regard to narrative requests at agency and MAH side.
342-344		Comment: 1. It is not clear to what extend MAHs are expected to screen product information authorised within EU for signals already potentially addressed. There is no central place for updated product information from EU countries, the MAHs have access to. Therefore monitoring of content of different product information from different MAHs and in different countries seems to be challenging for MAHs. Moreover, to decide if the wording as included in an authorised product information matches the current signal situation might be out of scope of MAHs and lead to differing product information. The process of transferring a validated signal to a product information update through formal variation implies to agree the wording among MAH, and the approval of the content by the Competent Authority. Therefore it could be more practical that the content of the text is harmonised and lead by the NCA in charge of the signal evaluation.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		2. In addition, there might be situations where the signal is included in other EU labels but the generic MAH has not enough data to sustain causality/submit safety variations. Proposed change: 1. To refer to product information published within EMA portal or originator SmPC, which also might not be harmonized within EU. 2. In this situation, access to case narratives seems to be crucial and should be granted
345-346		Comment: "The signal was not ***recently*** addressed by CA, MSs or by PRAC". A clear timeframe seems to be preferable to define what is considered "recently". Proposed change: To define a clear timeframe of minimum period for re-examination of an already raised signal, especially in view of the different timeframes of signal detection activities expected to be performed by MAHs of up to 6 months as outlined within GVP IX.
347-348		Comment: It is mentioned that when a signal originates from 'EudraVigilance Data', MAH should review the corresponding case narratives. Does it mean that case narrative review from EudraVigilance is not expected for signals originating from MAH's own data? If yes, then it is not aligned with what is mentioned in row 230-231. If no, then it is recommended to clarify the same in guidance. Proposed change (if any): Editorial: For more clarity lines 347 and 348 should be placed in middle of line 339.
355-357		Comment: The suggested timings may impose significant work load on generic MAHs without automated data analysis systems, e.g. every two weeks for actives under additional monitoring, no more than six months for

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		others.
368-373		Comment: Six months could be a short period for substances for which only few cases are received and/or there is a well-established safety profile. Proposed change: An extension of the periodicity up to 1 year for generic products with well-established safety profile (e.g. generic products for which PSUR is not required).
374		Comment: Each organisation should document the frequency of their monitoring of EudraVigilance data according to the identified risk, the potential risks and the need for additional information on medicinal products or active substances. It is not clear how and where (e.g. MAH internal process, e.g. SOP; PSMF) the rationale for the chosen periodicity should be documented and in what extend it is expected to be discussed. Also, with generic products, it seems that it would be preferable to have periodicity proposed for well-established products provided from the Agency. Proposed change: To clearly define expectations on documentation for rationale of periodicity and provide guidance for well-established products.
376-377		Comment: Does this process only refer to signals emerging from the monitoring of EV only, or to all signals detected by MAHs?
447 - following		Comment: Figure IX.2 explains the flow & timelines for confirming signal. Timelines and process how member states and agency comes back to the MAH who raised the signal is missing. We propose that, only after confirmation from PRAC/member state to MAH, the MAH should start variation procedure to avoid duplications of efforts.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
383-386 and 544		Comment: In case of an emerging safety issue, relevant competent Authorities of Member States and the Agency should be notified within 2 working days of becoming aware of the issue. This time seems to be challenging in view of signal validation, and assessment to MAHs, which is a pre-requisite to forward relevant information to the Agency and not to saturate the system by transmitting less urgent information. Also taking into account the need of requesting narratives as outlined in GVP IX.C.2.1. It is suggested to re-consider time frames in view of the need for generic companies to gather sufficient information to comply with the process of not saturate the system by transmitting less urgent information as outlined in IX.C.3.1, which is acknowledged. In addition, the term of "relevant Member States" should be clearly defined (e.g. approved MAs, ongoing MA, Lead MS, MAH has no approved MA in the relevant country). Also, it would be appreciated to receive a dedicated email address for all national competent authorities to receive emerging safety issue notifications. Proposed change: To clearly state when the 2 days start so that MAHs can comply with the proposed timelines and relevance: "This should be done within 2 working days **after signal validation, and assessment within the MAH signal management process**. ~~of becoming aware of the issue~~.
401-405		Comment: 1. It is outlined that variation should be submitted as soon as possible after a signal is validated but no later than 3 months after signal validations. 2. Signal validation is defined in 117-121 as" signal validation is the process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence to justify further analysis of the signal…" which seem not to include the supporting evidence for assessment and propose actions as outlined in 401. It is also not considered consistent that changes to the product information should be proposed after validation. 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')*
		1. It is proposed to extend the deadline for submission of safety variations up to 6 months for signals that qualify as non-important risks. This would allow more flexibility and synchronization with PSUR submissions. 2. Review of terminology to be aligned within the document. It is proposed to use signal evaluation/assessment.
409-412		Comment: 1. It should be noted that notification to relevant competent authority in case of missing information within the innovator SmPC is expected of numerous generic MAHs, leading to huge amount of requests for discussion at the relevant competent authority. This potentially may delay the process. It is proposed that MAHs should only use EV for evaluation of their own signals and rely on the signal detection process by EMA/MS for EV signals 2. It is proposed to liaise with the relevant competent authority in case the proposed change is not reflected in the innovator product information. Clarification is needed for the situation when the signal is included in another generic SmPC but not in the innovator´s. Also in case there is no innovator available advice should be given, e.g. what generic SmPC can be considered as reference instead. In addition, clarification about "relevant competent authorities" and contact details would be appreciated. Moreover, time frame for liaison with competent authority is not clearly stated. Proposed change: Reference is made to the proposal above in the "general comment" section.
416-423		Comment: It is stated that that validated signals for which there is sufficient evidence to propose changes to product information and/or RMP shall be included in PSUR, unless the MAH considers that a variation application should be submitted. Clarification or an example about this situation would be appreciable for MAHs to have clear guideline. Also, it is suggested to extend the timeline of due PSUR submission to the following 6 months after signal validation and assessment to allow more flexibility and synchronisation with PSUR submission.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
418		Comment: Terminology is not clear as it is referred to validated signal not to evaluate.
429-433		Comment: It mentions '….. all validated signals and emerging safety issues …should be reported in the PSUR.' PSUR requires discussion of closed signals too, hence it is recommended that the sentence is reworded to avoid subjective interpretation.
447		Comment: It is not clear how MAHs who closed the signal and did not take any other action are to be informed
452-454		In case a generic company is not involved in PSUR assessment, the information about the outcome of signal assessment is not available to that MAH. In that case, it may take more than 1 year since signal notification until update of innovator SmPC. The possibility of early information of generic MAH or a general access to all PSUSAs at the Agency´s side would be appreciated.
489		Comment: Referring to the recommendations of PRAC, it is stated within the first bullet that "no action is required…..other than routine pharmacovigilance". Does this mean this signal was closed and refuted?

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14-Oct-2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
Otsuka

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Line 21-30 The Agency provided specific questions in which it seeks specific feedback. Please see replies below in red text. Are the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders acceptable (see IX.C.2.1.)? **Yes** Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable (see IX.C.2.2.)? **Yes** Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable (see IX.C.3.)? **It is not clear, please refer to comment in "Specific Comment on text" lines 416-423**

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
117 - 152		The removal of the examples in the definition of Emerging Safety Issues and the fact that this topic is moved to module IX brings up the question whether out of stock situations are still in scope for as a potential Emerging Safety Issue. The focus seems to be on safety signals only now. Should out of stock situations for certain important medications (in terms of patient safety) for which there are no readily available alternatives not be reported as such anymore?
416 - 423		Comment: Please add clarifying text explaining further how a validated signal should be submitted to the EMA. Line 419-421 is not clear in explaining when a "variation application with supportive data should be submitted" in lieu of a PSUR being submitted 3 months after signal is validated Proposed change (if any):

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	PHARMIG, the association of the Austrian pharmaceutical industry, thanks for the opportunity to comment on the draft Rev. 1 of GVP Module IX.
	Questions on which the Agency seeks specific feedback by means of the public consultation: 1. Are the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders acceptable (see IX.C.2.1.)? These criteria have been developed to prevent unjustified download of case narratives, in relation to Annex C (Confidentiality Undertaking for Marketing Authorisation Holders) of the EudraVigilance Access Policy which aims at ensuring the protection of personal data. We cannot comment on this question because of lack of practical experience so far. 2. Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable (see IX.C.2.2.)? See specific comment on lines 372 – 375. 3. Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable (see IX.C.3.)? See our comment on line 439. The timelines should be consistent and aligned (3 months).
	The term "signal validation" is used throughout the document for the definition of a starting point for timelines like in Line 439 "This should be done as soon as possible and no later than 30 days after the signal is validated." or Line 401 "..as a result of signal validation.. no later than 3 months after the signal is validated." However, in accordance to the definition a signal validation is a process and timelines cannot refer to a process as they should refer to a clear starting point i.e when the MAH has completed his signal validation process and has concluded that the signal is confirmed by an established causal relationship and requiring further regulatory action.

Stakeholder number *(To be completed by the Agency)*	General comment
	It should be made more clear that by the MAH refuted signals do not need to be reported to the Agency and do not fall under the timelines. Of course they will be included in the PSUR Section 16.2 "signal evaluation".
	It should be specified as mentions "3 months if PSUR is due to be included in the PSUR", however as the DLP is 70 calendar days for PSURs with <12 months frequency and 90 calendar days (3 months) for PSURs with >12 months frequency were this information should be reflected as it occurs at or after the DLP ie if it should be presented in the late breaking news sections or elsewhere.
	It should be made more clear that this GVP Module is only applicable for EU signal detection process and signal confirmation by PRAC for a product and applicable to the marketing authorization in EU as also global active MAH have to conduct signal confirmation, analysis, assessment and recommendation ie if a new confirmed signal by the MAH needs to be implemented into the CCDS and therefore be reflected in the global labels.
	Emergent Safety Issue: Currently it is mentioned that within 2 working days of becoming aware of the issue the agency should be informed". However the term "becoming aware" is open for a broad interpretation and it should be better specified like after the MAH has confirmed the signal and decided on further actions. Further, for consistency reason also Regulation 536/2014 Art 54 (Clinical trials) should be considered stating "Urgent Safety Measure notification shall be made without undue delay but no **later than seven days** from the date the measures have been taken." Different timelines may result in confusion, especially if the emergent safety issue is related to a non-IMP or an IMP with a marketing authorization and investigated in or outside the authorized indications impacting the same target population for example.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
267-268		Comment: Professional judgement and flexibility should be applied throughout the process is currently stated. It should be specified that it should a professional scientific judgement and not for example any other professions judgement. Proposed change (if any): add highlighted text Professional scientific judgement and flexibility should be applied throughout the process.
290 -292		Comment: Documentation may be requested from marketing authorisation holders to demonstrate compliance with these requirements at any time, including justification / evidence for the steps taken and decisions made is currently mentioned, but not clarified under which circumstances and under which timelines. Further, this is captured in PV inspections. Proposed change (if any): delete ~~Documentation may be requested from marketing authorisation holders to demonstrate compliance with these requirements at any time, including justification / evidence for the steps taken and decisions made.~~
293-295		Comment: The wording is open for a broad interpretation on what a a specific trainings means. Further, in accordance to the GVP Module I and II and as all PV staff must be adequately be trained to be able to fulfil their PV obligations delegetated. Proposed change (if any): delete ~~Staff members should be specifically trained in signal management activities in accordance with their 294 roles and responsibilities~~
326 (Table)		Comment: The table shows that MAHs only carry out EV monitoring, signal detection and signal validation, and that NCAs and PRAC are the only parties who carry out signal confirmation, analysis, assessment and recommendation.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		However, global MAH in the global context will conduct signal confirmation/analysis/assessment and recommendation for any activity like inclusion in CCDS, investigator letters etc. also with regard to clinical trials in which a marketed product is used as IMP. It should be clarified that this is only related to EU MA and how will be the interaction if clinical trial are involved. Proposed change (if any): add highlighted text Signal analysis and prioritisation, assessment, recommendation with potential impact for the marketing authorization (ie. Labelling) in EU
332- 333		Comment: Signals should not be mixed up with risks for consistency reasons within this Module. A new signal can be a higher frequency or a change to a known safety concern or a new potential safety concern. Proposed change (if any): Such monitoring should be performed to determine whether there are new signals ~~or whether risks have changed and whether those risks have~~ which may have an adverse impact on the risk-benefit balance of the medicinal product(s)
356-375		Comment: The periodicity of signal monitoring should follow a risk-based approach like a PSUR frequency as outlined in the EURD list. The PSUR is per definition in GVP Modules the benefit-risk assessment document of the medicinal product. The PSUR frequency ie. EURD-List is a risk based approach on a regular benefit-risk assessment cycle based on the knowledge about the medicinal product. Signal detection periodicity should follow a similar risk-based approach and not been mandated bi-annually for all products and 2 weekly for products with additional monitoring except it is due to a PASS. However, also PAES should be considered in this context. Proposed change (if any): Adapt to a risk-based approach based on PSUR cycles and provide recommendations for signal detection ie. Monthly, Quarterly or annually.
372 – 375		It is recommended that the interval between reviews of EudraVigilance data should not exceed 6 months. Each organisation should document the frequency of their monitoring of EudraVigilance data (see also IX.B.5.).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Comment: More clarification on responsibilities of the MAH is required. What exactly should be screened by the MAH? Is there an additional benefit for the organisations in screening all active substances (duplication of work)? Proposed change (if any):
385-386		Comment: See also the general comment this should be aligned with the Regulation and more detailed specified. Proposed change (if any): add highlighted text This should be done within 7 calendar days ~~of becoming aware of the issue~~ after having fully evaluated the signal and having decided within the MAH on recommendation.
396-399		Proposed change (if any): Marketing authorisation holders should only communicate as emerging safety issues those ~~safety concerns~~ signals which meet the definition provided in IX.A, i.e. whose urgency and seriousness cannot permit any delay in handling, for instance ~~validated~~ fully evaluated signals warranting any further regulatory action as assessed by the MAH and that cannot wait up to 30 days for confirmation by Member States.
439		This should be done as soon as possible and no later than 30 days after the signal is validated. Comment: Timeline should be aligned to timelines for variations and PSURs (3 months). Proposed change (if any):
434-446		Comment: The Standalone signal notification currently refers to by the MAH refuted signals. This may result in only

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		providing a MeDDRA term like a PT or LLT. Further, it is not specified which documents may be requested by the Agency if a refuted signal is notified ie. Cumulative reviews or STR etc which are currently mostly requested by PRAC if a signal has been confirmed by PRAC. Proposed change (if any): Refuted signals should not be required to be sent to the Agency within 30 days after the full signal assessment and recommendation for refuting by the MAH and if this is the intent of the GVP Module another risk-based approach and a more specified timeframe with detailing of required documents should be considered.
527		IX.C.8. Transparency Comment: Please include recommendation that the "Advance notification of signals on the PRAC agenda" has to be sent to QPPV five days before the PRAC meeting. Proposed change (if any):
543-544		Comment: The process map shows if the evidence is not sufficient to propose changes to the product information and/or RMP (refuted signals) to be send within 30 days as standalone signal notification if the PSUR is not due within 3 months. What is the duplication with the PSUR GVP VII Section 16.2 as this will be at or after the DLP of the PSUR and the Annex for signals and the interference with 6-monthly PSURs? This seems to become an undue burden for MAH and it should be made clear that refuted signals need not to be reported within 30 days or a justification for this request been provided or on risk-based approach a cumulative list been provided ie annually. Proposed change (if any): -
547		Send list of confirmed signals to all QPPVs Comment:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		We welcome this requirement. However, as per today this is not yet executed by the Agency. Proposed change (if any):

Please add more rows if needed.

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<Date of submission>

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
Pierre Fabre

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
404		Comment: A risk based approach should be implemented instead of the unique timelines proposed for submission of variation. Proposed change (if any): We suggest to replace "no later than 3 months" by no later than 6 months or in 3 months depending on the criticity of the signal"
		Comment: Proposed change (if any):
		Comment: Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
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14 October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
PrimeVigilance Ltd.

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Could some specific aspects of signal detection for generic products and orphan drugs be added? The only highlighted difference for generic products is that they should liaise with the competent authority prior to submitting a variation that refers to the introduction of a change not reflected in the innovator product information. Should the generics also liaise with the competent authorities regarding the frequency of signal detection from EudraVigilance?

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')*
IX.C.2.1. 335 - 340		Agency Question: Are the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders acceptable? Proposed change (if any): Draft GVP Module VI already has added guidance that case narrative should not include information that could lead to the identification of the patient, including reference to healthcare professionals or treatment centres. It is suggested to also add to this guidance (GVP VI) that the narrative might be shared with other MAHs if needed for signal validation, and to therefore consider also omitting all reporter and sender identifiers from this data element.
IX.C.2.2. 355 - 374		Agency Question: Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable? Comment: Please clarify who will be deciding on the appropriate frequency of monitoring EudraVigilance data? Is it recommended the MAHs consult with PRAC on the appropriate frequency of monitoring each of their products? Proposed change (if any): For almost 2,500 products on the EURD list with PSUR frequency established to be every 4 years (or more) it is acceptable to monitor EudraVigilance once a year.
IX.C.3. 378 - 446		Agency Question: Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Comment: What is the acceptable timeframe to validate a signal? Do all MedDRA terms (e.g. PTs) that cross the defined threshold have to be validated or would it be sufficient to pick out the terms describing (unlisted) recognised medical entities? How is being aware of an ESI defined? Would that be the moment signal analysis is completed and conclusion that is it an ESI agreed upon with the company drug safety committee (which includes the QPPV) or some other moment? Proposed change (if any): /
IX.C.3.2. 409 - 412		Text in the proposed GVP IX: When the application refers to the introduction of a change not reflected in the innovator product information, marketing authorisation holders for generic products should liaise with the relevant competent authorities prior to the submission of such variation application to agree on the appropriate way to handle the potential amendment of the product information. Comment: How to identify the originator? Will a list of the originator product be posted on the EMA and HMA websites? Which competent authority to consult with - the PRAC rapporteur? Proposed change (if any): /

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
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Thursday, 06 October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
QuintilesIMS [redacted]

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	It would help the MAH to have a clear definition of terminologies regarding the signal management process in the revised Module IX, because changing these terminologies will have considerable impact of current well established MAH processes. Currently, a lot of MAH are using the following terminologies for the signal management process: 1. Signal Detection 2. Signal Validation and prioritisation (before validation a signal is named "potential signal", after validation a signal is either "not validated" or "validated". If prioritised, a signal can be an emerging safety issue. 3. Signal Evaluation: each validated signal is evaluated by the MAH considering all available data. The outcome of signal evaluation is either "signal refuted" or "risk" (either identified or potential). Also further actions are decided at signal evaluation, such as label change, conduct a PASS, etc.. Finally, to support this signal management process, MAH have also developed IT-validated audit-trailed tracking tools, which would need to be changed if terminology and/or signal steps in the GVP Module IX revision 1 are being amended. In the revised Module IX, it looks like the MAH are not responsible for the signal evaluation, whereas this step is a very important step in the MAH's strategic decision to evaluate the benefit-risk balance of its products.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 137-139		**Comment:** The signal management process at the MAH level should mirror the signal management process at PRAC level. At MAH level the following steps are part of signal management: signal detection, signal validation (including analysis and prioritization) and signal evaluation (synonym of signal assessment). Therefore I suggest that the definition of the signal assessment be generic and not for PRAC only. **Proposed change (if any):** ***Signal assessment ~~by the Pharmacovigilance Risk Assessment Committee (PRAC)~~*** Following ~~PRAC~~ initial analysis and prioritisation, the process of evaluating all available data relevant to a signal to determine the need for further action (e.g. any regulatory action (see IX.C.5.)).
Lines 188-190		**Comment:** For more clarity of signal management steps, and to be consistent with the terminology described in the definition section (see line 117), I suggest to change the section title to Signal validation (for your reference, in many MAH, evaluation is the term used for the actual "assessment" of a signal, therefore potentially leading to confusion of sequential signal management steps described in this GVP module IX revision 1). **Proposed change (if any):** ***IX.B.3. ~~Evaluation of the evidence supporting a s~~Signal validation*** The following elements should be considered when evaluating the evidence supporting a detected signal at signal validation:
Lines 235-244		**Comment:** There are several comments regarding this paragraph: 1) The decisions resulting from the "evaluation of the evidence supporting a signal" (=signal validation) are confusing in the context of the signal validation definition (see lines 117-121: "in order to verify that the available documentation contains sufficient evidence to justify further analysis of the signal"). According to this definition the signal validation decision should be: -**yes**, there is sufficient evidence to justify further analysis" or -**no**, there is not sufficient evidence".

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		2) The decision options are also confusing in the context of the Signal Confirmation definition (which is the step, at PRAC level, after validation) (see lines 128-129: "The fact that a signal is confirmed does not imply that a causal relationship has been established,"). It seems preliminary to establish a causal association when such decision, as per definition of signal confirmation, would not yet be made at the signal confirmation step. 3) The term "CLOSED" signal is currently used to inform on the status of a validated signal, rather than a decision on a signal (see example in module VII on PSUR such as the following sentence:"Signals arising from clinical trial sources should be tabulated in PSUR section 15 ("Overview on signals: new, ongoing or closed")"). An **ongoing** signal would be a validated signal for which evaluation/assessment is ongoing; a **closed** signal would be a validated signal for which the evaluation / assessment was completed. I therefore would not use the term "CLOSED" for a signal for which the validation decision was "Signal Not Validated". **Proposed change (if any):** The evaluation of the evidence supporting a signal may involve several rounds of expert discussions and different levels of decision-making, within individual organisations. This may result in various decisions, such as: • ~~closing the signal~~ Signal Not Validated, when the available data do not support a causal relationship (the signal may be re-opened at a later stage if new evidence arises) or when there is sufficient information on the association in the product information; • Keep under review: monitoring the signal by reviewing new information from ICSRs or the scientific literature at appropriate time intervals to determine whether the new data are supportive of a causal relationship; • Signal Validated: proceed with a thorough evaluation/assessment of the signal for recommendation of further ~~proposing~~ actions such as changes to the product information by means of a variation~~, if there is sufficient evidence of a causal relationship~~.
Lines 377-378		**Comments** According to this section the MAH will not do the signal evaluation / assessment for any products marketed in EU. As mentioned in the general comments section, this step is a very important step in the MAH's strategic decision to evaluate the benefit-risk balance of its products. I would therefore reconsider this approach.
Lines 377-378		**Comments** How should the MAH inform EMA of a validated signal? Any dedicated email address? And specific format? Please add some explanation in this section.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Proposed changes (if any): ***IX.C.3. Notifications and procedural options for signals validated by the marketing authorisation holder in the EU*** This section outlines the options marketing authorisation holders have to inform competent authorities of signals they have validated.
Lines 401-407		**Comments** As per definition of signal validation, at signal validation the MAH decides whether there is sufficient evidence to justify further assessment. The MAH is not deciding whether the product information should be changes at signal validation. This would occur only after thorough evaluation of the signal, taking into account all available sources of information. Therefore, I would suggest to change the wording in this section, to reflect these sequential steps. **Proposed changes (if any):** When, following signal validation and as a result of signal evaluation/assessment ~~validation~~, a marketing authorisation holder considers the evidence sufficient to propose changes to the product information and/or the RMP, they should submit an appropriate variation application to the relevant competent authorities (if urgent attention is required, see IX.C.3.1.). This should be done as soon as possible and no later than 3 months after the signal is validated. In such instances, a standalone signal notification (see IX.C.3.4.) is not required, as the proposed changes and supportive evidence will be assessed by the relevant competent authorities within the variation procedure.
Lines 429-432		**Comments** Terminology is very important in the signal management process. This sentence reflect my understanding of the signal management steps and I wanted to highlight it positively, in light of my previous comments regarding terminology. "Regardless of whether they have been reported in accordance with the processes described in sections IX.C.3.1., IX.C.3.2. and IX.C.3.4., all validated signals and emerging safety issues for which the evaluation was concluded during the reporting interval of a PSUR, or are under evaluation at the time of a PSUR data lock point, should be reported in that PSUR (PSUR sections 15 and 16) (see GVP Module VII)." **Proposed Changed (if any):** None
Lines 434-438		**Comments:** Based on the signal management steps, following signal validation (if the signal is validated), the signal will be evaluated by the MAH, therfore timing should be set taking into account the signal evaluation step. The GVP

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		Module IX rev 1 states the following (reworded as per my understanding) 1-If the validated signal is an emerging safety issue, the MAH will notify EMA within 2 days following signal validation. 2-If the validated signal (following evaluation) warrants a label update, the MAH will submit a variation within 3 months following validation. 3-If validated signal ongoing or closed within 3 months of PSUR submission deadline, then signal evaluation is reported in the frame of the PSUR. 4-If the validated signal, following evaluation, isn't an ESI nor warrants label update, nor occurs within PSUR period, then it needs to be submitted as a stand-alone signal notification within 30 days after signal validation. The 30 day timeline versus the 3 month timeline is confusing. Why would a label update notification have longer timelines than the fourth option?. In these options (2,3 and 4) the MAH would need to perform an evaluation, which would take the same time. Also the decision to update the label or not would be made following evaluation so to be able to comply with GVP Module IX rev 1, MAH would need to always perform the signal evaluation within 30 days of validation. **Proposed Changes (if any)** **IX.C.3.4. Standalone signal notification** When a validated signal, following evaluation/assessment, does not meet any of the conditions outlined in IX.C.3.1., IX.C.3.2. or IX.C.3.3., the marketing authorisation holder should complete the signal validation form[15] available on the European medicines web-portal and send it via [functional e-mail address tbc][16] to the Agency and national competent authorities. This should be done as soon as possible and no later than 30 days [recommend to revise timelines according to my comments above] after the signal is validated.
Line 447-449		**Comment:** As per Appendix 1, PRAC is confirming only those signals not submitted within a variation nor a PSUR or considered as an emerging safety issue. Is that correct? **Proposed changes (if any):** ***IX.C.4. Signal confirmation by Member States*** Within 30 days of receipt of a validated signal, the PRAC rapporteur or (lead) Member State, as applicable, should confirm or not the signal, i.e. decide whether or not it should undergo PRAC analysis and prioritisation at the subsequent meeting (see IX.A.).

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
Global Corporate Headquarters: [redacted] European Business Office: [redacted] Regeneron is a fully-integrated, biopharmaceutical company that produces and develops biological drugs, including recombinant fusion proteins and monoclonal antibodies, for the treatment of a broad array of diseases and conditions, particularly for the treatment of serious medical conditions. Our research is conducted on a global level and includes clinical development in EU Member States.

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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)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	Regeneron appreciates the opportunity to comment on the Agency's revised 'draft guideline on Good Pharmacovigilance Practices (GVP) Module IX – Signal management.' Overall, we agree that the guideline would be useful to stakeholders in clarifying expectations in the detection and management of safety signals. Our proposed comments, contained herein, are meant to assist the Agency in improving the clarity of the guidance so that stakeholders may have consistent interpretations of Agency expectations.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Section IX.C.2.1, Principles for access: Line 341		Comment: Reference is made to an "electronic reaction monitoring report". However, there is no definition for this term in section IX.A. We request that the Agency add a definition for "electronic reaction monitoring report" to the Terminology section to ensure that Sponsors and MAHs are aligned with the interpretation and Agency expectations. This definition should specify the data points included in the report along with a list of criteria regarding accessibility. Proposed change (if any):
		Comment: Proposed change (if any):

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
Seqirus

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
118-119		Comment: The current description of signal validation in lines 118-119 implies that further analysis of the signal is required to determine if the validated signal represents a "true signal". Proposed change (if any): The term "validated signal" should be provided in IX.A.1 to avoid potential interpretation errors. This is especially important considering that the timeline for safety variation application to the CAs for validated signals, which have sufficient evidence to propose changes to the product information and/or the RMP, is dependent on when the signal was validated.
122-130		Comment: A new term "signal confirmation" is included in the revision 1. However, this step seems primarily intended for the CA or the Rapporteur appointed by the PRAC to determine whether or not a validated signal notified should be analysed and prioritised by the PRAC. It is unclear as to whether this step is applicable to MAHs. In addition, the MAH may proceed with necessary actions to address a validated signal even before it is reviewed by PRAC for confirmation. It is appreciated that the PRAC may be reviewing the signal on an EU level, but what would the implications be should an MAH-validated signal be deemed "unconfirmed" by PRAC after a recommended action has already been implemented by the MAH?

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
401-404		In general, the term "signal confirmation' is misleading as it tends to implies that the validated signal is confirmed as "true signal" following evaluation of evidence supporting a signal (IX.B.3). Proposed change (if any): Differentiate the requirements of the MAH from those of the CAs for each component of signal management process. The term "confirmed signal" should be provided in IX.A.1. A clear differentiation of validated vs confirmed signal would be very beneficial. Comment: For seasonal influenza vaccines which require Annual Strain Update variations (during which time other variations are not permissible), submission of an updated RMP or Labelling variation with standard evaluation timelines may not be possible without impacting the timely availability of product to the market ahead of the peak influenza period. Consideration by EMA in these situations is suggested. Proposed change (if any): Suggest additional sentence after Paragraph 1 of IX.C.3.2, Line 405: For seasonal products requiring annual updates (e.g. influenza vaccines), where the labelling or RMP variation is required just prior to the season or at the same time as the annual update, discussions with competent authorities on submission, evaluation and implementation timelines should start as early as possible.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
416-423		Comment: For seasonal influenza vaccines with an annual PSUR DLP of 15 March and submission date by 24 May, it may not be practical to seek endorsement of a proposed amendment to the product information for a safety signal (if validated within 3 months of submission), if implementation for the next Northern Hemisphere season is recommended, as the PSUR evaluation timeline would not be aligned. It is acknowledged that the option of a labelling variation in most cases will therefore be the only practical option.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14-Oct-2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
UCB Biopharma sprl

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	RE: Questions on which the Agency seeks specific feedback by means of the public consultation: **Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable (see IX.C.2.2.)?** **Comment**: It is difficult for the Marketing Authorization Holders to assess whether or not the recommendations regarding the frequency of monitoring of EudraVigilance database are acceptable (from 2 week/monthly to 6 months maximum, risk based approach) since we don't know which data will be provided, in which format, and what will be the process to be followed by the Marketing Authorization Holders for the screening of data in EudraVigilance. The revised module makes reference to a guidance related to EudraVigilance outputs and the EudraVigilance Data Analysis System (EVDAS) available in the EVDAS Report Manual and in MAH's level 1 access via EVDAS. However, it is also mentioned that these documents are under development and that references will be provided in the final revised GVP module IX. Flexibility of frequency in line with the parameters outlined is considered appropriate but final conclusion on appropriateness of proposed timelines will depend on the documents aforementioned.
	RE: Questions on which the Agency seeks specific feedback by means of the public consultation: **Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable (see IX.C.3.)?** **Comment**: There is some confusion about the scope of the revised module due to different wordings used throughout the document. Is the guidance limited to signals detected in Eudravigilance or is it applicable for all signals detected by the Marketing Authorization Holder, i.e. signals detected from any sources, including Eudravigilance? There is a mix between general definitions about the signal management process (signal, signal management process, signal detection, signal validation) and definitions that are specific to the signal management process in EudraVigilance (signal confirmation, signal analysis and prioritization by the Pharmacovigilance Risk Assessment Committee (PRAC), signal assessment by the Pharmacovigilance Risk Assessment Committee (PRAC), Lead Member State for signal management).

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')*
122-130		**Comment**: Definition for Signal Confirmation-The definition is specific to the signal management process in EudraVigilance and can bring confusion as the verbiage 'confirmed signal' would mean to many, that a causal association has been confirmed. And although there is a statement to say this is not the case, the verbiage is unnecessarily misleading. **Proposed change** (if any): Re-wording of the term to prevent any confusion with the signal assessment step eg Validation confirmation or Validation endorsement
317-318		**Comment**: It is mentioned that "each organisation should validate and prioritise signals they have detected (or that have been brought to their attention) from any source, including EudraVigilance". However, in Table IX.1. Roles and responsibilities within the EU signal management process only include the responsibilities and roles in EudraVigilance and MAH role is only to validate.
490-491		**Comment**: The 'following' PSUR may be in the process of being written and there is currently no direct mechanism to do this in the PSUR, as the current PSUR requirements appear to indicate a summary of activities done within the interval. Is a revised GVP Module VII expected? Or is the meaning intended to be as shown in proposed change below? **Proposed change** (if any): the marketing authorisation holder should *report* ~~review~~ the signal in the following PSUR or submit an ad-hoc PSUR *if eg the time interval before the next PSUR is considered too long or if a PSUR is in the process of being written at the time of the recommendation.*
543-545		**Comment**: Given the roles and responsibilities assigned to MAH in Table IX, this figure is confusing. MAH cannot decide on whether there is sufficient evidence to propose changes to product information and/or RMP without doing a detailed assessment such as is described by the processes for the PRAC during the signal analysis and prioritization step, i.e. "an initial analysis of the potential impact of the signal on patient and public health and the risk-benefit balance of the concerned medicinal product(s)" as mentioned in section

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
		IX.A.1.Terminology **Comment**: Figure suggests that further assessment by MAH is not required for emerging safety issues which is unrealistic, given the signal evaluation and prioritisation process in place at MAH level and the wealth of information MAH may hold from multiple sources. If notification at such an early stage is mandatory, there has to be a clear process for the MAH to be able to communicate with EMA with follow up information to verify or refute the signal.
549-552		**Comment**: In case of discrepant assessment/confirmation by the various authorities, is it confirmed that the PRAC are the final arbitrator?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
Xendo-Vigilex

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	When we compare section IX.B in this revised version of the Module with the same section in the previous module we notice there is a change in terminology that we find very confusing. Steps in the process used to be signal detection, signal validation, signal analysis and prioritisation, signal assessment, recommendation for action and exchange of information and it was clear that the MAH was also involved with all steps of this process. Now the steps in the process covered in IX.B are signal detection, evaluation of the evidence supporting a signal, and signal prioritisation. Especially considering the terminology part of the module it seems that besides the newly added terminology of signal confirmation, signal analysis and prioritisation and signal assessment, covered in IX.C, are now solely performed by the PRAC. We would recommend to further clarify the terminology with a focus on validation, confirmation and evaluation and to further clarify the role of MAH and PRAC in different steps. There now seems to be a mix up of validation with evaluation. Especially with signal detection methods such as disproportionality analysis, which may result in a certain amount of noise, a first (quick) validation is needed to exclude false positive signals from further evaluation. Further in section IX.B, the focus should be on the signal management process from the perspective of the MAH. This can then be connected to the process at the EU level as described in IX.C.
	Subsection IX.B.5 Quality requirements is now at the end of the section IX.B. We suggest to place this more in the beginning of the section. The quality requirements are really important and actually reflect that you can only have a good signal management process if you first define a good strategy which may differ dependent on the products in your portfolio and so frequency and methods used may not be the same for all products etc. Only if this is in place the signal management process can appropriately function.
	Comments in relation to Q2 Agency We are a consultancy organisation and can therefore not answer the question whether the recommendations regarding the frequency of monitoring of EV data are acceptable. We think it is important for the Agency when considering the input for this question from MAHs to carefully consider the differences there may be dependent on e.g. product portfolio (a.o. generics, innovative, time on the market). Currently, the Module seems to give the possibility to choose own frequency for monitoring Eudravigilance data, provided a good rationale is given, but with a minimum of once every 6 months. We would suggest not to describe a minimum. We think the most important thing should be for a MAH to determine how signal detection in EV fits in/adds value to the MAH strategy for signal

Stakeholder number *(To be completed by the Agency)*	General comment
	management, considering the profile of the product and methods of signal detection (e.g. using company database or external database(s)). Further, considering the EMA and national competent authorities also do signal detection in EV on a regular basis, it should be clear how signal detection by the MAH in EV would add to what is already done by the competent authorities, in order to prevent duplicate work.
	Comments in relation to Q3 Agency Again we are a consultancy organisation and can therefore not answer the question whether the proposed timelines and modalities for communication of emerging safety issues and validated signals by MAH are acceptable. With regard to clarity of the guidance, we feel more clarity should be provided in terms of timelines for communication of validated signals. Considering the signal validation form is not available yet, it is difficult to make an assessment if it would be feasible for MAHs to report all validated signals (which do not fall under the category of emerging safety issues and do not have sufficient evidence to product information and/or RMP) within a timeline of 30 days.
	There are many flowcharts in the appendices, that can be helpful but also confusing. First, we suggest to make sure that the flowcharts are adequately updated to avoid confusion about terminology as indicated above. Second, we suggest to make clear which flowcharts are provided to MAH mainly for purpose of transparency to make clear how things function at EU level and which ones are really meant to further clarify the responsibilities of the MAH and this should be a limited number of process maps.

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')*
147-152 382-399		Comment: We agree with the revised definition and the process of emerging safety issues added to this Module which was previously included in Module VI. Proposed change (if any): We suggest to add some examples for a clear and consistent understanding among MAHs about what should and what should not be considered as an emerging safety issue.
188		Comment: This is an example of a place in the text where there seems to be confusion between signal validation and evaluation. See also general comment about this above. Proposed change (if any): Consider to clarify the terminology in this heading. What is meant here, evaluation or validation?
436		Comment: When will the signal validation form be available and implemented on European medicine web portal?
400-405		Comment: This is an example of a place in the text where there seems to be confusion between signal validation and evaluation. Only after a full evaluation, a MAH can make a proper assessment whether changes to product information are needed. See also general comment about this above. Proposed change (if any): Propose to update the first and the last sentence of this paragraph as follows: When as a result of singal validation, **and subsequent evaluation**, a marketing authorisation holder consideres the evidence sufficient to propose..... This should be done as soon as possible and no later than 3 months after the signal is validated**/evaluated.**

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
543		Comment: In figure IX.1 some timelines are indicated. However, the figure starts at the stage of a validated signal and does not include the prior step detection of a signal. Proposed change (if any): Consider to further clarify in this figure and/or text of Module what are acceptable timelines for step from detection to validation.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Module IX – Signal management (EMA/827661/2011 Rev. 1)

Comments from:

Name of organisation or individual
Zeincro Hellas S.A

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	
	As a general comment we would like to state that there is no provision for what a MAH should do when a signal is received from non-EU Adverse Drug Reaction Data and which data do not consist an emerging safety issue.	
	Response to Question 1 (lines 22-23): Yes, we consider the proposed criteria acceptable.	
	Response to Question 2 (lines 27-28): Smaller generic companies have limited ADRs in their database, where in the case that their product is included in the additional monitoring list it will be a burden to have to monitor the data every two weeks. We propose that for the said companies, a monitoring every six months could occur and be sufficient.	
	Response to Question 3 lines 29-30): Yes, we consider the proposed timelines clear and acceptable	

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')*
118		Comment: the word "detected" before the word signal may be confusing. The definition of a signal includes the validation process. Therefore, it has already been detected, Proposed change (if any): please consider entering the word "potential" prior to the word signal or delete word signal and add the phrase "detected information that may lead to potential signal.
368		Comment: the apostrophe after the word "weeks" is possibly a typographical error. Proposed change (if any):
372		Comment: Please clarify to whom "it is recommended" that the interval between reviews should not exceed 6 months Proposed change (if any): please consider entering the parties involved for the recommendation. Ex: It is recommended that MAHs and NCAs have an interval between reviews of EudraVigilance data that does not exceed 6 months.
543-544 (Figure IX.1)		Comment: in the current GVP VI (Rev1) it mentions that emerging safety issues " *should be notified as emerging safety issues in writing to the competent authorities in Member States where the medicinal product is authorised and to the Agency"* in the current diagram the top right box mentions that the issue should be send to EMA and "relevant national competent authorities". We would like to propose that the "relevant national" authorities are clarified. We could adopt the same phrasing as in the current GVP VI (rev 1). Proposed change (if any): see comment above

Please add more rows if needed.